VERIFICATION OF TRANSLATION

German Patent Application No. 102 54 601.0
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am the translator of the document attached and I state that the following is a true translation to the best of my knowledge and belief of German Patent Application No. 102 54 601.0 filed on November 22, 2002.

DATED: April 13, 2007

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GENETIC PRODUCTS DIFFERENTIALLY EXPRESSED IN TUMORS AND THE USE THEREOF

Despite interdisciplinary approaches and exhaustive use of classical therapeutic procedures, cancers are still among the leading causes of death. More recent therapeutic concepts aim at incorporating the patient's immune system into the overall therapeutic concept by using recombinant tumor vaccines and other specific measures such as antibody therapy. A prerequisite for the success of such a strategy is the recognition of tumor-specific or tumor-associated antigens or epitopes by the patient's immune system whose effector functions are to be interventionally enhanced. Tumor cells biologically differ substantially from their nonmalignant cells of origin. These differences are due to genetic alterations acquired during tumor development and result, inter alia, also in the formation of qualitatively or quantitatively altered molecular structures in the cancer cells. Tumor-associated structures of this kind which are recognized by the specific immune system of the tumor-harboring host are referred to as tumor-associated antigens. The specific recognition of tumor-associated antigens involves cellular and humoral mechanisms which are two functionally interconnected units: $CD4^+$ and $CD8^+$ T lymphocytes recognize the processed antigens presented on the molecules of the MHC (major histocompatibility complex) classes II and I, respectively, while B lymphocytes produce circulating antibody molecules which bind directly to unprocessed antigens. The potential clinical-therapeutical importance of tumor-associated antigens results from the fact that the recognition of antigens on neoplastic cells by the immune system leads to the initiation of cytotoxic effector mechanisms and, in the presence of T helper cells, can cause elimination of the cancer cells (Pardoll, *Nat. Med.* 4:525-31, 1998). Accordingly, a

central aim of tumor immunology is to molecularly define these structures. The molecular nature of these antigens has been enigmatic for a long time. Only after development of appropriate cloning techniques has it been possible to screen cDNA expression libraries of tumors systematically for tumor-associated antigens by analyzing the target structures of cytotoxic T lymphocytes (CTL) (van der Bruggen et al., *Science* 254:1643-7, 1991) or by using circulating autoantibodies (Sahin et al., *Curr. Opin. Immunol.* 9:709-16, 1997) as probes. To this end, cDNA expression libraries were prepared from fresh tumor tissue and recombinantly expressed as proteins in suitable systems. Immunoeffectors isolated from patients, namely CTL clones with tumor-specific lysis patterns, or circulating autoantibodies were utilized for cloning the respective antigens.

In recent years a multiplicity of antigens have been defined in various neoplasias by these approaches. However, the probes utilized for antigen identification in the classical methods illustrated above are immunoeffectors (circulating autoantibodies or CTL clones) from patients usually having already advanced cancer. A number of data indicate that tumors can lead, for example, to tolerization and anergization of T cells and that, during the course of the disease, especially those specificities which could cause effective immune recognition are lost from the immunoeffector repertoire. Current patient studies have not yet produced any solid evidence of a real action of the previously found and utilized tumor-associated antigens. Accordingly, it cannot be ruled out that proteins evoking spontaneous immune responses are the wrong target structures.

It was the object of the present invention to provide target structures for a diagnosis and therapy of cancers.

According to the invention, this object is achieved by the subject matter of the claims.

According to the invention, a strategy for identifying and providing antigens expressed in association with a tumor and the nucleic acids coding therefor was pursued. This strategy is based on the fact that particular genes which are expressed in an organ specific manner, e.g. exclusively in colon, lung or kidney tissue, are reactivated also in tumor cells of the respective organs and moreover in tumor cells of other tissues in an ectopic and forbidden manner. First, data mining produces a list as complete as possible of all known organ-specific genes which are then evaluated for their aberrant activation in different tumors by expression analyses by means of specific RT-PCR. Data mining is a known method of identifying tumor-associated genes. In the conventional strategies, however, transcriptoms of normal tissue libraries are usually subtracted electronically from tumor tissue libraries, with the assumption that the remaining genes are tumor-specific (Schmitt et al., *Nucleic Acids Res.* 27:4251-60, 1999; Vasmatzis et al., *Proc. Natl. Acad. Sci. USA.* 95:300-4, 1998; Scheurle et al., *Cancer Res.* 60:4037-43, 2000).

The concept of the invention, which has proved much more successful, however, is based on utilizing data mining for electronically extracting all organ-specific genes and then evaluating said genes for expression in tumors.

The invention thus relates in one aspect to a strategy for identifying tissue-specific genes differentially expressed in tumors. Said strategy combines data mining of public sequence libraries ("*in silico*") with subsequent evaluating laboratory-experimental ("wet bench") studies.

According to the invention, a combined strategy based on two different bioinformatic scripts enabled new tumor genes to be identified. These have previously been classified as being purely organ-specific. The finding that these genes are aberrantly activated in tumor cells allows them to be assigned a substantially new quality with functional implications. According to the invention, these tumor-associated genes and the genetic products encoded thereby were identified and provided independently of an immunogenic action.

The tumor-associated antigens identified according to the invention have an amino acid sequence encoded by a nucleic acid which is selected from the group consisting of (a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of (SEQ ID NOs: 1-8, 41-44, 51-59, 84), a part or derivative thereof, (b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions, (c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and (d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c). In a preferred embodiment, a tumor-associated antigen identified according to the invention has an amino acid sequence encoded by a nucleic acid which is selected from the group consisting of (SEQ ID NOs: 1-8, 41-44, 51-59, 84). In a further preferred embodiment, a tumor-associated antigen identified according to the invention comprises an amino acid sequence selected from the group consisting of (SEQ ID NOs: 9-19, 45-48, 60-66, 85), a part or derivative thereof.

The present invention generally relates to the use of tumor-associated antigens identified according to the invention or of parts thereof, of nucleic acids coding therefor or of nucleic acids directed against said coding nucleic acids or of antibodies directed against

the tumor-associated antigens identified according to the invention or parts thereof for therapy and diagnosis. This utilization may relate to individual but also to combinations of two or more of these antigens, functional fragments, nucleic acids, antibodies, etc., in one embodiment also in combination with other tumor-associated genes and antigens for diagnosis, therapy and progress control.

Preferred diseases for a therapy and/or diagnosis are those in which one or more of the tumor-associated antigens identified according to the invention are selectively expressed or abnormally expressed.

The invention also relates to nucleic acids and genetic products which are expressed in association with a tumor cell and which are produced by altered splicing (splice variants) of known genes or altered translation using alternative open reading frames. These nucleic acids comprise the sequences according to (SEQ ID NOs: 3-5) of the sequence listing. Moreover, the genetic products comprise sequences according to (SEQ ID NOs: 10, 12-14) of the sequence listing. The splice variants of the invention can be used according to the invention as targets for diagnosis and therapy of tumor diseases.

In a further embodiment, the invention relates to a protein sequence according to (SEQ ID NO: 10) which is encoded by an alternative open reading frame identified according to the invention and differs from the previously described protein sequence (SEQ ID NO: 9) in additional 85 amino acids at the N terminus of the protein.

Very different mechanisms may cause splice variants to be produced, for example

- utilization of variable transcription initiation sites
- utilization of additional exons

- complete or incomplete splicing out of single or two or more exons,
- splice regulator sequences altered via mutation (deletion or generation of new donor/acceptor sequences),
- incomplete elimination of intron sequences.

Altered splicing of a gene results in an altered transcript sequence (splice variant). Translation of a splice variant in the region of its altered sequence results in an altered protein which may be distinctly different in the structure and function from the original protein. Tumor-associated splice variants may produce tumor-associated transcripts and tumor-associated proteins/antigens. These may be utilized as molecular markers both for detecting tumor cells and for therapeutic targeting of tumors. Detection of tumor cells, for example in blood, serum, bone marrow, sputum, bronchial lavage, bodily secretions and tissue biopsies, may be carried out according to the invention, for example, after extraction of nucleic acids by PCR amplification with splice variant-specific oligonucleotides. In particular, pairs of primers are suitable as oligonucleotides at least one of which binds to the region of the splice variant which is tumor-associated under stringent conditions. In particular, according to the invention, oligonucleotides described under (SEQ ID NOs: 34-36) are suitable. According to the invention, all sequence-dependent detection systems are suitable for detection. These are, apart from PCR, for example gene chip/microarray systems, Northern blot, RNAse protection assays (RDA) and others. All detection systems have in common that detection is based on a specific hybridization with at least one splice variant-specific nucleic acid sequence. However, tumor cells may also be detected according to the invention by antibodies which recognize a specific epitope encoded by the splice variant. Said antibodies may be

prepared by using for immunization peptides which are specific for said splice variant. Suitable for immunization are particularly the amino acids whose epitopes are distinctly different from the variant(s) of the genetic product, which is (are) preferably produced in healthy cells. Detection of the tumor cells with antibodies may be carried out here on a sample isolated from the patient or as imaging with intravenously administered antibodies. In addition to diagnostic usability, splice variants having new or altered epitopes are attractive targets for immunotherapy. The epitopes of the invention may be utilized for targeting therapeutically active monoclonal antibodies or T lymphocytes. In passive immunotherapy, antibodies or T lymphocytes which recognize splice variant-specific epitopes are adoptively transferred here. As in the case of other antigens, antibodies may be generated also by using standard technologies (immunization of animals, panning strategies for isolation of recombinant antibodies) with utilization of polypeptides which include these epitopes. Alternatively, it is possible to utilize for immunization nucleic acids coding for oligo- or polypeptides which contain said epitopes. Various techniques for in vitro or in vivo generation of epitope-specific T lymphocytes are known and have been described in detail (for example Kessler JH, et al. 2001, Sahin et al., 1997) and are likewise based on utilizing oligo- or polypeptides which contain the splice variant-specific epitopes or nucleic acids coding for said oligo- or polypeptides. Oligo- or polypeptides which contain the splice variant-specific epitopes or nucleic acids coding for said polypeptides may also be used as pharmaceutically active substances in active immunotherapy (vaccination, vaccine therapy).

In one aspect, the invention relates to a pharmaceutical composition comprising an agent which recognizes the tumor-associated antigen identified

according to the invention and which is preferably selective for cells which have expression or abnormal expression of a tumor-associated antigen identified according to the invention. In particular embodiments, said agent may cause induction of cell death, reduction in cell growth, damage to the cell membrane or secretion of cytokines and preferably have a tumor-inhibiting activity. In one embodiment, the agent is an antisense nucleic acid which hybridizes selectively with the nucleic acid coding for the tumor-associated antigen. In a further embodiment, the agent is an antibody which binds selectively to the tumor-associated antigen, in particular a complement-activated or toxin conjugated antibody which binds selectively to the tumor-associated antigen. In a further embodiment, the agent comprises two or more agents which each selectively recognize different tumor-associated antigens, at least one of which is a tumor-associated antigen identified according to the invention. Recognition needs not be accompanied directly with inhibition of activity or expression of the antigen. In this aspect of the invention, the antigen selectively limited to tumors preferably serves as a label for recruiting effector mechanisms to this specific location. In a preferred embodiment, the agent is a cytotoxic T lymphocyte which recognizes the antigen on an HLA molecule and lyses the cells labeled in this way. In a further embodiment, the agent is an antibody which binds selectively to the tumor-associated antigen and thus recruits natural or artificial effector mechanisms to said cell. In a further embodiment, the agent is a T helper lymphocyte which enhances effector functions of other cells specifically recognizing said antigen.

In one aspect, the invention relates to a pharmaceutical composition comprising an agent which inhibits expression or activity of a tumor-associated antigen identified according to the invention. In a

preferred embodiment, the agent is an antisense nucleic acid which hybridizes selectively with the nucleic acid coding for the tumor-associated antigen. In a further embodiment, the agent is an antibody which binds selectively to the tumor-associated antigen. In a further embodiment, the agent comprises two or more agents which each selectively inhibit expression or activity of different tumor-associated antigens, at least one of which is a tumor-associated antigen identified according to the invention.

The invention furthermore relates to a pharmaceutical composition which comprises an agent which, when administered, selectively increases the amount of complexes between an HLA molecule and a peptide epitope from the tumor-associated antigen identified according to the invention. In one embodiment, the agent comprises one or more components selected from the group consisting of (i) the tumor-associated antigen or a part thereof, (ii) a nucleic acid which codes for said tumor-associated antigen or a part thereof, (iii) a host cell which expresses said tumor-associated antigen or a part thereof, and (iv) isolated complexes between peptide epitopes from said tumor-associated antigen and an MHC molecule. In one embodiment, the agent comprises two or more agents which each selectively increase the amount of complexes between MHC molecules and peptide epitopes of different tumor-associated antigens, at least one of which is a tumor-associated antigen identified according to the invention.

The invention furthermore relates to a pharmaceutical composition which comprises one or more components selected from the group consisting of (i) a tumor-associated antigen identified according to the invention or a part thereof, (ii) a nucleic acid which codes for a tumor-associated antigen identified according to the invention or for a part thereof, (iii)

an antibody which binds to a tumor-associated antigen identified according to the invention or to a part thereof, (iv) an antisense nucleic acid which hybridizes specifically with a nucleic acid coding for a tumor-associated antigen identified according to the invention, (v) a host cell which expresses a tumor-associated antigen identified according to the invention or a part thereof, and (vi) isolated complexes between a tumor-associated antigen identified according to the invention or a part thereof and an HLA molecule.

A nucleic acid coding for a tumor-associated antigen identified according to the invention or for a part thereof may be present in the pharmaceutical composition in an expression vector and functionally linked to a promoter.

A host cell present in a pharmaceutical composition of the invention may secrete the tumor-associated antigen or the part thereof, express it on the surface or may additionally express an HLA molecule which binds to said tumor-associated antigen or said part thereof. In one embodiment, the host cell expresses the HLA molecule endogenously. In a further embodiment, the host cell expresses the HLA molecule and/or the tumor-associated antigen or the part thereof in a recombinant manner. The host cell is preferably nonproliferative. In a preferred embodiment, the host cell is an antigen-presenting cell, in particular a dendritic cell, a monocyte or a macrophage.

An antibody present in a pharmaceutical composition of the invention may be a monoclonal antibody. In further embodiments, the antibody is a chimeric or humanized antibody, a fragment of a natural antibody or a synthetic antibody, all of which may be produced by combinatory techniques. The antibody may be coupled to a therapeutically or diagnostically useful agent.

An antisense nucleic acid present in a pharmaceutical composition of the invention may comprise a sequence of 6-50, in particular 10-30, 15-30 and 20-30, contiguous nucleotides of the nucleic acid coding for the tumor-associated antigen identified according to the invention.

In further embodiments, a tumor-associated antigen, provided by a pharmaceutical composition of the invention either directly or via expression of a nucleic acid, or a part thereof binds to MHC molecules on the surface of cells, said binding preferably causing a cytolytic response and/or inducing cytokine release.

A pharmaceutical composition of the invention may comprise a pharmaceutically compatible carrier and/or an adjuvant. The adjuvant may be selected from saponin, GM-CSF, CpG nucleotides, RNA, a cytokine or a chemokine. A pharmaceutical composition of the invention is preferably used for the treatment of a disease characterized by selective expression or abnormal expression of a tumor-associated antigen. In a preferred embodiment, the disease is cancer.

The invention furthermore relates to methods of treating or diagnosing a disease characterized by expression or abnormal expression of one of more tumor-associated antigens. In one embodiment, the treatment comprises administering a pharmaceutical composition of the invention.

In one aspect, the invention relates to a method of diagnosing a disease characterized by expression or abnormal expression of a tumor-associated antigen identified according to the invention. The method comprises detection of (i) a nucleic acid which codes for the tumor-associated antigen or of a part thereof

and/or (ii) detection of the tumor-associated antigen or of a part thereof, and/or (iii) detection of an antibody to the tumor-associated antigen or to a part thereof and/or (iv) detection of cytotoxic or T helper lymphocytes which are specific for the tumor-associated antigen or for a part thereof in a biological sample isolated from a patient. In particular embodiments, detection comprises (i) contacting the biological sample with an agent which binds specifically to the nucleic acid coding for the tumor-associated antigen or to the part thereof, to said tumor-associated antigen or said part thereof, to the antibody or to cytotoxic or T helper lymphocytes specific for the tumor-associated antigen or parts thereof, and (ii) detecting the formation of a complex between the agent and the nucleic acid or the part thereof, the tumor-associated antigen or the part thereof, the antibody or the cytotoxic or T helper lymphocytes. In one embodiment, the disease is characterized by expression or abnormal expression of two or more different tumor-associated antigens and detection comprises detection of two or more nucleic acids coding for said two or more different tumor-associated antigens or of parts thereof, detection of two or more different tumor-associated antigens or of parts thereof, detection of two or more antibodies binding to said two or more different tumor-associated antigens or to parts thereof or detection of two or more cytotoxic or T helper lymphocytes specific for said two or more different tumor-associated antigens. In a further embodiment, the biological sample isolated from the patient is compared to a comparable normal biological sample.

In a further aspect, the invention relates to a method for determining regression, course or onset of a disease characterized by expression or abnormal expression of a tumor-associated antigen identified according to the invention, which method comprises monitoring a sample from a patient who has said disease

or is suspected of falling ill with said disease, with respect to one or more parameters selected from the group consisting of (i) the amount of nucleic acid which codes for the tumor-associated antigen or of a part thereof, (ii) the amount of the tumor-associated antigen or a part thereof, (iii) the amount of antibodies which bind to the tumor-associated antigen or to a part thereof, and (iv) the amount of cytolytic T cells or T helper cells which are specific for a complex between the tumor-associated antigen or a part thereof and an MHC molecule. The method preferably comprises determining the parameter(s) in a first sample at a first point in time and in a further sample at a second point in time and in which the course of the disease is determined by comparing the two samples. In particular embodiments, the disease is characterized by expression or abnormal expression of two or more different tumor-associated antigens and monitoring comprises monitoring (i) the amount of two or more nucleic acids which code for said two or more different tumor-associated antigens or of parts thereof, and/or (ii) the amount of said two or more different tumor-associated antigens or of parts thereof, and/or (iii) the amount of two or more antibodies which bind to said two or more different tumor-associated antigens or to parts thereof, and/or (iv) the amount of two or more cytolytic T cells or of T helper cells which are specific for complexes between said two or more different tumor-associated antigens or of parts thereof and MHC molecules.

According to the invention, detection of a nucleic acid or of a part thereof or monitoring the amount of a nucleic acid or of a part thereof may be carried out using a polynucleotide probe which hybridizes specifically to said nucleic acid or said part thereof or may be carried out by selective amplification of said nucleic acid or said part thereof. In one embodiment, the polynucleotide probe comprises a

sequence of 6-50, in particular 10-30, 15-30 and 20-30, contiguous nucleotides of said nucleic acid.

In particular embodiments, the tumor-associated antigen to be detected or the part thereof is present intracellularly or on the cell surface. According to the invention, detection of a tumor-associated antigen or of a part thereof or monitoring the amount of a tumor-associated antigen or of a part thereof may be carried out using an antibody binding specifically to said tumor-associated antigen or said part thereof.

In further embodiments, the tumor-associated antigen to be detected or the part thereof is present in a complex with an MHC molecule, in particular an HLA molecule.

According to the invention, detection of an antibody or monitoring the amount of antibodies may be carried out using a protein or peptide binding specifically to said antibody.

According to the invention, detection of cytolytic T cells or of T helper cells or monitoring the amount of cytolytic T cells or of T helper cells which are specific for complexes between an antigen or a part thereof and MHC molecules may be carried out using a cell presenting the complex between said antigen or said part thereof and an MHC molecule.

The polynucleotide probe, the antibody, the protein or peptide or the cell, which is used for detection or monitoring, is preferably labeled in a detectable manner. In particular embodiments, the detectable marker is a radioactive marker or an enzymic marker. T lymphocytes may additionally be detected by detecting their proliferation, their cytokine production, and their cytotoxic activity triggered by specific stimulation with the complex of MHC and tumor-associated antigen or parts thereof. T lymphocytes may

also be detected via a recombinant MHC molecule or else a complex of two or more MHC molecules which are loaded with the particular immunogenic fragment of one or more of the tumor-associated antigens and which can identify the specific T lymphocytes by contacting the specific T cell receptor.

In a further aspect, the invention relates to a method of treating, diagnosing or monitoring a disease characterized by expression or abnormal expression of a tumor-associated antigen identified according to the invention, which method comprises administering an antibody which binds to said tumor-associated antigen or to a part thereof and which is coupled to a therapeutic or diagnostic agent. The antibody may be a monoclonal antibody. In further embodiments, the antibody is a chimeric or humanized antibody or a fragment of a natural antibody.

The invention also relates to a method of treating a patient having a disease characterized by expression or abnormal expression of a tumor-associated antigen identified according to the invention, which method comprises (i) removing a sample containing immunoreactive cells from said patient, (ii) contacting said sample with a host cell expressing said tumor-associated antigen or a part thereof, under conditions which favor production of cytolytic T cells against said tumor-associated antigen or a part thereof, and (iii) introducing the cytolytic T cells into the patient in an amount suitable for lysing cells expressing the tumor-associated antigen or a part thereof. The invention likewise relates to cloning the T cell receptor of cytolytic T cells against the tumor-associated antigen. Said receptor may be transferred to other T cells which thus receive the desired specificity and, as under (iii), may be introduced into the patient.

In one embodiment, the host cell endogenously expresses an HLA molecule. In a further embodiment, the host cell recombinantly expresses an HLA molecule and/or the tumor-associated antigen or the part thereof. The host cell is preferably nonproliferative. In a preferred embodiment, the host cell is an antigen-presenting cell, in particular a dendritic cell, a monocyte or a macrophage.

In a further aspect, the invention relates to a method of treating a patient having a disease characterized by expression or abnormal expression of a tumor-associated antigen, which method comprises (i) identifying a nucleic acid which codes for a tumor-associated antigen identified according to the invention and which is expressed by cells associated with said disease, (ii) transfecting a host cell with said nucleic acid or a part thereof, (iii) culturing the transfected host cell for expression of said nucleic acid (this is not obligatory when a high rate of transfection is obtained), and (iv) introducing the host cells or an extract thereof into the patient in an amount suitable for increasing the immune response to the patient's cells associated with the disease. The method may further comprise identifying an MHC molecule presenting the tumor-associated antigen or a part thereof, with the host cell expressing the identified MHC molecule and presenting said tumor-associated antigen or a part thereof. The immune response may comprise a B cell response or a T cell response. Furthermore, a T cell response may comprise production of cytolytic T cells and/or T helper cells which are specific for the host cells presenting the tumor-associated antigen or a part thereof or specific for cells of the patient which express said tumor-associated antigen or a part thereof.

The invention also relates to a method of treating a disease characterized by expression or abnormal

expression of a tumor-associated antigen identified according to the invention, which method comprises (i) identifying cells from the patient which express abnormal amounts of the tumor-associated antigen, (ii) isolating a sample of said cells, (iii) culturing said cells, and (iv) introducing said cells into the patient in an amount suitable for triggering an immune response to the cells.

Preferably, the host cells used according to the invention are nonproliferative or are rendered nonproliferative. A disease characterized by expression or abnormal expression of a tumor-associated antigen is in particular cancer.

The present invention furthermore relates to a nucleic acid selected from the group consisting of (a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of (SEQ ID NOs: 3-5), a part or derivative thereof, (b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions, (c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and (d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c). The invention furthermore relates to a nucleic acid, which codes for a protein or polypeptide comprising an amino acid sequence selected from the group consisting of (SEQ ID NOs: 10, 12-14), a part or derivative thereof.

In a further aspect, the invention relates to promoter sequences of nucleic acids of the invention. These sequences may be functionally linked to another gene, preferably in an expression vector, and thus ensure selective expression of said gene in appropriate cells.

In a further aspect, the invention relates to a recombinant nucleic acid molecule, in particular DNA or RNA molecule, which comprises a nucleic acid of the

invention.

The invention also relates to host cells which contain a nucleic acid of the invention or a recombinant nucleic acid molecule comprising a nucleic acid of the invention.

The host cell may also comprise a nucleic acid coding for a HLA molecule. In one embodiment, the host cell endogenously expresses the HLA molecule. In a further embodiment, the host cell recombinantly expresses the HLA molecule and/or the nucleic acid of the invention or a part thereof. Preferably, the host cell is nonproliferative. In a preferred embodiment, the host cell is an antigen-presenting cell, in particular a dendritic cell, a monocyte or a macrophage.

In a further embodiment, the invention relates to oligonucleotides which hybridize with a nucleic acid identified according to the invention and which may be used as genetic probes or as "antisense" molecules. Nucleic acid molecules in the form of oligonucleotide primers or competent samples, which hybridize with a nucleic acid identified according to the invention or parts thereof, may be used for finding nucleic acids which are homologous to said nucleic acid identified according to the invention. PCR amplification, Southern and Northern hybridization may be employed for finding homologous nucleic acids. Hybridization may be carried out under low stringency, more preferably under medium stringency and most preferably under high stringency conditions. The term "stringent conditions" according to the invention refers to conditions which allow specific hybridization between polynucleotides.

In a further aspect, the invention relates to a protein, polypeptide or peptide which is encoded by a nucleic acid selected from the group consisting of (a) a nucleic acid which comprises a nucleic acid sequence

selected from the group consisting of SEQ ID NOs: 3-5, a part or derivative thereof, (b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions, (c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and (d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c). In a preferred embodiment, the invention relates to a protein or polypeptide or peptide which comprises an amino acid sequence selected from the group consisting of (SEQ ID NOs: 10, 12-14), a part or derivative thereof.

In a further aspect, the invention relates to an immunogenic fragment of a tumor-associated antigen identified according to the invention. Said fragment preferably binds to a human HLA receptor or to a human antibody. A fragment of the invention preferably comprises a sequence of at least 6, in particular at least 8, at least 10, at least 12, at least 15, at least 20, at least 30 or at least 50, amino acids.

In a further aspect, the invention relates to an agent which binds to a tumor-associated antigen identified according to the invention or to a part thereof. In a preferred embodiment, the agent is an antibody. In further embodiments, the antibody is a chimeric, a humanized antibody or an antibody produced by combinatory techniques or is a fragment of an antibody. Furthermore, the invention relates to an antibody which binds selectively to a complex of (i) a tumor-associated antigen identified according to the invention or a part thereof and (ii) an MHC molecule to which said tumor-associated antigen identified according to the invention or said part thereof binds, with said antibody not binding to (i) or (ii) alone. An antibody of the invention may be a monoclonal antibody. In further embodiments, the antibody is a chimeric or humanized antibody or a fragment of a natural antibody.

The invention furthermore relates to a conjugate between an agent of the invention which binds to a tumor-associated antigen identified according to the invention or to a part thereof or an antibody of the invention and a therapeutic or diagnostic agent. In one embodiment, the therapeutic or diagnostic agent is a toxin.

In a further aspect, the invention relates to a kit for detecting expression or abnormal expression of a tumor-associated antigen identified according to the invention, which kit comprises agents for detection (i) of the nucleic acid which codes for the tumor-associated antigen or of a part thereof, (ii) of the tumor-associated antigen or of a part thereof, (iii) of antibodies which bind to the tumor-associated antigen or to a part thereof, and/or (iv) of T cells which are specific for a complex between the tumor-associated antigen or a part thereof and an MHC molecule. In one embodiment, the agents for detection of the nucleic acid or the part thereof are nucleic acid molecules for selective amplification of said nucleic acid, which comprise, in particular a sequence of 6-50, in particular 10-30, 15-30 and 20-30, contiguous nucleotides of said nucleic acid.

Detailed description of the invention

According to the invention, genes are described which are expressed in tumor cells selectively or aberrantly and which are tumor-associated antigens.

According to the invention, these genes or their derivatives are preferred target structures for therapeutic approaches. Conceptionally, said therapeutic approaches may aim at inhibiting the activity of the selectively expressed tumor-associated genetic product. This is useful, if said aberrant respective selective expression is functionally

important in tumor pathogenecity and if its ligation is accompanied by selective damage of the corresponding cells. Other therapeutic concepts contemplate tumor-associated antigens as labels which recruit effector mechanisms having cell-damaging potential selectively to tumor cells. Here, the function of the target molecule itself and its role in tumor development are totally irrelevant.

"Derivative" of a nucleic acid means according to the invention that single or multiple nucleotide substitutions, deletions and/or additions are present in said nucleic acid. Furthermore, the term "derivative" also comprises chemical derivatization of a nucleic acid on a nucleotide base, on the sugar or on the phosphate. The term "derivative" also comprises nucleic acids which contain nucleotides and nucleotide analogs not occurring naturally.

According to the invention, a nucleic acid is preferably deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). Nucleic acids comprise according to the invention genomic DNA, cDNA, mRNA, recombinantly produced and chemically synthesized molecules. According to the invention, a nucleic acid may be present as a single-stranded or double-stranded and linear or covalently circularly closed molecule.

The nucleic acids described according to the invention have preferably been isolated. The term "isolated nucleic acid" means according to the invention that the nucleic acid was (i) amplified *in vitro*, for example by polymerase chain reaction (PCR), (ii) recombinantly produced by cloning, (iii) purified, for example by cleavage and gel-electrophoretic fractionation, or (iv) synthesized, for example by chemical synthesis. An isolated nucleic acid is a nucleic acid which is available for manipulation by recombinant DNA techniques.

A nucleic acid is "complementary" to another nucleic acid if the two sequences are capable of hybridizing and forming a stable duplex with one another, with hybridization preferably being carried out under conditions which allow specific hybridization between polynucleotides (stringent conditions). Stringent conditions are described, for example, in Molecular Cloning: A Laboratory Manual, J. Sambrook et al., Editors, 2nd Edition, Cold Spring Harbor Laboratory press, Cold Spring Harbor, New York, 1989 or Current Protocols in Molecular Biology, F.M. Ausubel et al., Editors, John Wiley & Sons, Inc., New York and refer, for example, to hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinylpyrrolidone, 0.02% bovine serum albumin, 2.5 mM NaH_2PO_4 (pH 7), 0.5% SDS, 2 mM EDTA). SSC is 0.15 M sodium chloride/0.15 M sodium citrate, pH 7. After hybridization, the membrane to which the DNA has been transferred is washed, for example, in 2 × SSC at room temperature and then in 0.1-0.5 × SSC/0.1 × SDS at temperatures of up to 68°C.

According to the invention, complementary nucleic acids have at least 40%, in particular at least 50%, at least 60%, at least 70%, at least 80%, at least 90% and preferably at least 95%, at least 98% or at least 99%, identical nucleotides.

Nucleic acids coding for tumor-associated antigens may, according to the invention, be present alone or in combination with other nucleic acids, in particular heterologous nucleic acids. In preferred embodiments, a nucleic acid is functionally linked to expression control sequences or regulatory sequences which may be homologous or heterologous with respect to said nucleic acid. A coding sequence and a regulatory sequence are "functionally" linked to one another, if they are covalently linked to one another in such a way that

expression or transcription of said coding sequence is under the control or under the influence of said regulatory sequence. If the coding sequence is to be translated into a functional protein, then, with a regulatory sequence functionally linked to said coding sequence, induction of said regulatory sequence results in transcription of said coding sequence, without causing a frame shift in the coding sequence or said coding sequence not being capable of being translated into the desired protein or peptide.

The term "expression control sequence" or "regulatory sequence" comprises according to the invention promoters, enhancers and other control elements which regulate expression of a gene. In particular embodiments of the invention, the expression control sequences can be regulated. The exact structure of regulatory sequences may vary as a function of the species or cell type, but generally comprises 5'untranscribed and 5'untranslated sequences which are involved in initiation of transcription and translation, respectively, such as TATA box, capping sequence, CAAT sequence, and the like. More specifically, 5'untranscribed regulatory sequences comprise a promoter region which includes a promoter sequence for transcriptional control of the functionally linked gene. Regulatory sequences may also comprise enhancer sequences or upstream activator sequences.

Thus, on the one hand, the tumor-associated antigens illustrated herein may be combined with any expression control sequences and promoters. On the other hand, however, the promoters of the tumor-associated genetic products illustrated herein may, according to the invention, be combined with any other genes. This allows the selective activity of these promoters to be utilized.

According to the invention, a nucleic acid may furthermore be present in combination with another nucleic acid which codes for a polypeptide controlling secretion of the protein or polypeptide encoded by said nucleic acid from a host cell. According to the invention, a nucleic acid may also be present in combination with another nucleic acid which codes for a polypeptide causing the encoded protein or polypeptide to be anchored on the cell membrane of the host cell or compartmentalized into particular organelles of said cell. Similarly, a combination with a nucleic acid is possible which represents a reporter gene or any "tag".

In a preferred embodiment, a recombinant DNA molecule is according to the invention a vector, where appropriate with a promoter, which controls expression of a nucleic acid, for example a nucleic acid coding for a tumor-associated antigen of the invention. The term "vector" is used here in its most general meaning and comprises any intermediary vehicle for a nucleic acid which enables said nucleic acid, for example, to be introduced into prokaryotic and/or eukaryotic cells and, where appropriate, to be integrated into a genome. Vectors of this kind are preferably replicated and/or expressed in the cells. An intermediary vehicle may be adapted, for example, to the use in electroporation, in bombardment with microprojectiles, in liposomal administration, in the transfer with the aid of agrobacteria or in insertion via DNA or RNA viruses. Vectors comprise plasmids, phagemids or viral genomes.

The nucleic acids coding for a tumor-associated antigen identified according to the invention may be used for transfection of host cells. Nucleic acids here mean both recombinant DNA and RNA. Recombinant RNA may be prepared by in-vitro transcription of a DNA template. Furthermore, it may be modified by stabilizing sequences, capping and polyadenylation prior to application. According to the invention, the term "host

cell" relates to any cell which can be transformed or transfected with an exogenous nucleic acid. The term "host cells" comprises according to the invention prokaryotic (e.g. *E. coli*) or eukaryotic cells (e.g. dendritic cells, B cells, CHO cells, COS cells, K562 cells, yeast cells and insect cells). Particular preference is given to mammalian cells such as cells from humans, mice, hamsters, pigs, goats, primates. The cells may be derived from a multiplicity of tissue types and comprise primary cells and cell lines. Specific examples comprise keratinocytes, peripheral blood leukocytes, stem cells of the bone marrow and embryonic stem cells. In further embodiments, the host cell is an antigen-presenting cell, in particular a dendritic cell, monocyte or a macrophage. A nucleic acid may be present in the host cell in the form of a single copy or of two or more copies and, in one embodiment, is expressed in the host cell.

According to the invention, the term "expression" is used in its most general meaning and comprises the production of RNA or of RNA and protein. It also comprises partial expression of nucleic acids. Furthermore, expression may be carried out transiently or stably. Preferred expression systems in mammalian cells comprise pcDNA3.1 and pRc/CMV (Invitrogen, Carlsbad, CA), which contain a selectable marker such as a gene imparting resistance to G418 (and thus enabling stably transfected cell lines to be selected) and the enhancer-promoter sequences of cytomegalovirus (CMV).

In those cases of the invention in which an HLA molecule presents a tumor-associated antigen or a part thereof, an expression vector may also comprise a nucleic acid sequence coding for said HLA molecule. The nucleic acid sequence coding for the HLA molecule may be present on the same expression vector as the nucleic acid coding for the tumor-associated antigen or the

part thereof, or both nucleic acids may be present on different expression vectors. In the latter case, the two expression vectors may be cotransfected into a cell. If a host cell expresses neither the tumor-associated antigen or the part thereof nor the HLA molecule, both nucleic acids coding therefor are transfected into the cell either on the same expression vector or on different expression vectors. If the cell already expresses the HLA molecule, only the nucleic acid sequence coding for the tumor-associated antigen or the part thereof can be transfected into the cell.

The invention also comprises kits for amplification of a nucleic acid coding for a tumor-associated antigen. Such kits comprise, for example, a pair of amplification primers which hybridize to the nucleic acid coding for the tumor-associated antigen. The primers preferably comprise a sequence of 6-50, in particular 10-30, 15-30 and 20-30 contiguous nucleotides of the nucleic acid and are nonoverlapping, in order to avoid the formation of primer dimers. One of the primers will hybridize to one strand of the nucleic acid coding for the tumor-associated antigen, and the other primer will hybridize to the complementary strand in an arrangement which allows amplification of the nucleic acid coding for the tumor-associated antigen.

"Antisense" molecules or "antisense" nucleic acids may be used for regulating, in particular reducing, expression of a nucleic acid. The term "antisense molecule" or "antisense nucleic acid" refers according to the invention to an oligonucleotide which is an oligoribonucleotide, oligodeoxyribonucleotide, modified oligoribonucleotide or modified oligodeoxyribonucleotide and which hybridizes under physiological conditions to DNA comprising a particular gene or to mRNA of said gene, thereby inhibiting transcription of said gene and/or translation of said

mRNA. According to the invention, an "antisense molecule" also comprises a construct which contains a nucleic acid or a part thereof in reverse orientation with respect to its natural promoter. An antisense transcript of a nucleic acid or of a part thereof may form a duplex with the naturally occurring mRNA specifying the enzyme and thus prevent accumulation of or translation of the mRNA into the active enzyme. Another possibility is the use of ribozymes for inactivating a nucleic acid. Antisense oligonucleotides preferred according to the invention have a sequence of 6-50, in particular 10-30, 15-30 and 20-30, contiguous nucleotides of the target nucleic acid and preferably are fully complementary to the target nucleic acid or to a part thereof.

In preferred embodiments, the antisense oligonucleotide hybridizes with an N-terminal or 5′ upstream site such as a translation initiation site, transcription initiation site or promoter site. In further embodiments, the antisense oligonucleotide hybridizes with a 3′untranslated region or mRNA splicing site.

In one embodiment, an oligonucleotide of the invention consists of ribonucleotides, deoxyribonucleotides or a combination thereof, with the 5′ end of one nucleotide and the 3′ end of another nucleotide being linked to one another by a phosphodiester bond. These oligonucleotides may be synthesized in the conventional manner or produced recombinantly.

In preferred embodiments, an oligonucleotide of the invention is a "modified" oligonucleotide. Here, the oligonucleotide may be modified in very different ways, without impairing its ability to bind its target, in order to increase, for example, its stability or therapeutic efficacy. According to the invention, the term "modified oligonucleotide" means an oligonucleotide in which (i) at least two of its

nucleotides are linked to one another by a synthetic internucleoside bond (i.e. an internucleoside bond which is not a phosphodiester bond) and/or (ii) a chemical group which is usually not found in nucleic acids is covalently linked to the oligonucleotide. Preferred synthetic internucleoside bonds are phosphorothioates, alkyl phosphonates, phosphorodithioates, phosphate esters, alkyl phosphonothioates, phosphoramidates, carbamates, carbonates, phosphate triesters, acetamidates, carboxymethyl esters and peptides.

The term "modified oligonucleotide" also comprises oligonucleotides having a covalently modified base and/or sugar. "Modified oligonucleotides" comprise, for example, oligonucleotides with sugar residues which are covalently bound to low molecular weight organic groups other than a hydroxyl group at the 3′ position and a phosphate group at the 5′ position. Modified oligonucleotides may comprise, for example, a 2′-O-alkylated ribose residue or another sugar instead of ribose, such as arabinose.

Preferably, the proteins and polypeptides described according to the invention have been isolated. The terms "isolated protein" or "isolated polypeptide" mean that the protein or polypeptide has been separated from its natural environment. An isolated protein or polypeptide may be in an essentially purified state. The term "essentially purified" means that the protein or polypeptide is essentially free of other substances with which it is associated in nature or *in vivo*.

Such proteins and polypeptides may be used, for example, in producing antibodies and in an immunological or diagnostic assay or as therapeutics. Proteins and polypeptides described according to the invention may be isolated from biological samples such as tissue or cell homogenates and may also be expressed

recombinantly in a multiplicity of pro- or eukaryotic expression systems.

For the purposes of the present invention, "derivatives" of a protein or polypeptide or of an amino acid sequence comprise amino acid insertion variants, amino acid deletion variants and/or amino acid substitution variants.

Amino acid insertion variants comprise amino- and/or carboxy-terminal fusions and also insertions of single or two or more amino acids in a particular amino acid sequence. In the case of amino acid sequence variants having an insertion, one or more amino acid residues are inserted into a particular site in an amino acid sequence, although random insertion with appropriate screening of the resulting product is also possible. Amino acid deletion variants are characterized by the removal of one or more amino acids from the sequence. Amino acid substitution variants are characterized by at least one residue in the sequence being removed and another residue being inserted in its place. Preference is given to the modifications being in positions in the amino acid sequence which are not conserved between homologous proteins or polypeptides. Preference is given to replacing amino acids with other ones having similar properties such as hydrophobicity, hydrophilicity, electronegativity, volume of the side chain and the like (conservative substitution). Conservative substitutions, for example, relate to the exchange of one amino acid with another amino acid listed below in the same group as the amino acid to be substituted:

1. small aliphatic, nonpolar or slightly polar residues: Ala, Ser, Thr (Pro, Gly)
2. negatively charged residues and their amides: Asn, Asp, Glu, Gln
3. positively charged residues: His, Arg, Lys

4. large aliphatic, nonpolar residues: Met, Leu, Ile, Val (Cys)
5. large aromatic residues: Phe, Tyr, Trp.

Owing to their particular part in protein architecture, three residues are shown in brackets. Gly is the only residue without a side chain and thus imparts flexibility to the chain. Pro has an unusual geometry which greatly restricts the chain. Cys can form a disulfide bridge.

The amino acid variants described above may be readily prepared with the aid of known peptide synthesis techniques such as, for example, by solid phase synthesis (Merrifield, 1964) and similar methods or by recombinant DNA manipulation. Techniques for introducing substitution mutations at predetermined sites into DNA which has a known or partially known sequence are well known and comprise M13 mutagenesis, for example. The manipulation of DNA sequences for preparing proteins having substitutions, insertions or deletions, is described in detail in Sambrook et al. (1989), for example.

According to the invention, "derivatives" of proteins, polypeptides or peptides also comprise single or multiple substitutions, deletions and/or additions of any molecules associated with the enzyme, such as carbohydrates, lipids and/or proteins, polypeptides or peptides. The term "derivative" also extends to all functional chemical equivalents of said proteins, polypeptides or peptides.

According to the invention, a part or fragment of a tumor-associated antigen has a functional property of the polypeptide from which it has been derived. Such functional properties comprise the interaction with antibodies, the interaction with other polypeptides or proteins, the selective binding of nucleic acids and an

enzymatic activity. A particular property is the ability to form a complex with HLA and, where appropriate, generate an immune response. This immune response may be based on stimulating cytotoxic or T helper cells. A part or fragment of a tumor-associated antigen of the invention preferably comprises a sequence of at least 6, in particular at least 8, at least 10, at least 12, at least 15, at least 20, at least 30 or at least 50, consecutive amino acids of the tumor-associated antigen.

A part or a fragment of a nucleic acid coding for a tumor-associated antigen relates according to the invention to the part of the nucleic acid, which codes at least for the tumor-associated antigen and/or for a part or a fragment of said tumor-associated antigen, as defined above.

The isolation and identification of genes coding for tumor-associated antigens also make possible the diagnosis of a disease characterized by expression of one or more tumor-associated antigens. These methods comprise determining one or more nucleic acids which code for a tumor-associated antigen and/or determining the encoded tumor-associated antigens and/or peptides derived therefrom. The nucleic acids may be determined in the conventional manner, including by polymerase chain reaction or hybridization with a labeled probe. Tumor-associated antigens or peptides derived therefrom may be determined by screening patient antisera with respect to recognizing the antigen and/or the peptides. They may also be determined by screening T cells of the patient for specificities for the corresponding tumor-associated antigen.

The present invention also enables proteins binding to tumor-associated antigens described herein to be isolated, including antibodies and cellular binding partners of said tumor-associated antigens.

According to the invention, particular embodiments ought to involve providing "dominant negative" polypeptides derived from tumor-associated antigens. A dominant negative polypeptide is an inactive protein variant which, by way of interacting with the cellular machinery, displaces an active protein from its interaction with the cellular machinery or which competes with the active protein, thereby reducing the effect of said active protein. For example, a dominant negative receptor which binds to a ligand but does not generate any signal as response to binding to the ligand can reduce the biological effect of said ligand. Similarly, a dominant negative catalytically inactive kinase which usually interacts with target proteins but does not phosphorylate said target proteins may reduce phosphorylation of said target proteins as response to a cellular signal. Similarly, a dominant negative transcription factor which binds to a promoter site in the control region of a gene but does not increase transcription of said gene may reduce the effect of a normal transcription factor by occupying promoter binding sites, without increasing transcription.

The result of expression of a dominant negative polypeptide in a cell is a reduction in the function of active proteins. The skilled worker may prepare dominant negative variants of a protein, for example, by conventional mutagenesis methods and by evaluating the dominant negative effect of the variant polypeptide.

The invention also comprises substances such as polypeptides which bind to tumor-associated antigens. Such binding substances may be used, for example, in screening assays for detecting tumor-associated antigens and complexes of tumor-associated antigens with their binding partners and in the purification of said tumor-associated antigens and of complexes thereof

with their binding partners. Such substances may also be used for inhibiting the activity of tumor-associated antigens, for example by binding to such antigens.

The invention therefore comprises binding substances such as, for example, antibodies or antibody fragments, which are capable of selectively binding to tumor-associated antigens. Antibodies comprise polyclonal and monoclonal antibodies which are produced in the conventional manner.

It is known that only a small part of an antibody molecule, the paratope, is involved in binding of the antibody to its epitope (cf. Clark, W.R. (1986), *The Experimental Foundations of Modern Immunology*, Wiley & Sons, Inc., New York; Roitt, I. (1991), *Essential Immunology*, 7th Edition, Blackwell Scientific Publications, Oxford). The pFc' and Fc regions are, for example, effectors of the complement cascade but are not involved in antigen binding. An antibody from which the pFc' region has been enzymatically removed or which has been produced without the pFc' region, referred to as $F(ab')_2$ fragment, carries both antigen binding sites of a complete antibody. Similarly, an antibody from which the Fc region has been enzymatically removed or which has been produced without said Fc region, referred to as Fab fragment, carries one antigen binding site of an intact antibody molecule. Furthermore, Fab fragments consist of a covalently bound light chain of an antibody and part of the heavy chain of said antibody, referred to as Fd. The Fd fragments are the main determinants of antibody specificity (a single Fd fragment can be associated with up to ten different light chains, without altering the specificity of the antibody) and Fd fragments, when isolated, retain the ability to bind to an epitope.

Located within the antigen-binding part of an antibody are complementary-determining regions (CDRs) which

interact directly with the antigen epitope and framework regions (FRs) which maintain the tertiary structure of the paratope. Both the Fd fragment of the heavy chain and the light chain of IgG immunoglobulins contain four framework regions (FR1 to FR4) which are separated in each case by three complementary-determining regions (CDR1 to CDR3). The CDRs and, in particular, the CDR3 regions and, still more particularly, the CDR3 region of the heavy chain are responsible to a large extent for antibody specificity.

Non-CDR regions of a mammalian antibody are known to be able to be replaced by similar regions of antibodies with the same or a different specificity, with the specificity for the epitope of the original antibody being retained. This made possible the development of "humanized" antibodies in which nonhuman CDRs are covalently linked to human FR and/or Fc/pFc' regions to produce a functional antibody.

For example, WO 92/04381 describes the production and use of humanized murine RSV antibodies in which at least part of the murine FR regions have been replaced with FR regions of a human origin. Antibodies of this kind, including fragments of intact antibodies with antigen-binding capability, are often referred to as "chimeric" antibodies.

The invention also provides $F(ab')_2$, Fab, Fv, and Fd fragments of antibodies, chimeric antibodies, in which the Fc and/or FR and/or CDR1 and/or CDR2 and/or light chain-CDR3 regions have been replaced with homologous human or nonhuman sequences, chimeric $F(ab')_2$-fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain-CDR3 regions have been replaced with homologous human or nonhuman sequences, chimeric Fab-fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain-CDR3 regions have been replaced with homologous human or nonhuman sequences, and

chimeric Fd-fragment antibodies in which the FR and/or CDR1 and/or CDR2 regions have been replaced with homologous human or nonhuman sequences. The invention also comprises single-chain antibodies.

The invention also comprises polypeptides which bind specifically to tumor-associated antigens. Polypeptide binding substances of this kind may be provided, for example, by degenerate peptide libraries which may be prepared simply in solution in an immobilized form or as phage-display libraries. It is likewise possible to prepare combinatorial libraries of peptides with one or more amino acids. Libraries of peptoids and nonpeptidic synthetic residues may also be prepared.

Phage display may be particularly effective in identifying binding peptides of the invention. In this connection, for example, a phage library is prepared (using, for example, the M13, fd or lambda phages) which presents inserts of from 4 to about 80 amino acid residues in length. Phages are then selected which carry inserts which bind to the tumor-associated antigen. This process may be repeated via two or more cycles of a reselection of phages binding to the tumor-associated antigen. Repeated rounds result in a concentration of phages carrying particular sequences. An analysis of DNA sequences may be carried out in order to identify the sequences of the expressed polypeptides. The smallest linear portion of the sequence binding to the tumor-associated antigen may be determined. The "two-hybrid system" of yeast may also be used for identifying polypeptides which bind to a tumor-associated antigen. Tumor-associated antigens described according to the invention or fragments thereof may be used for screening peptide libraries, including phage-display libraries, in order to identify and select peptide binding partners of the tumor-associated antigens. Such molecules may be used, for example, for screening assays, purification protocols,

for interference with the function of the tumor-associated antigen and for other purposes known to the skilled worker.

The antibodies described above and other binding molecules may be used, for example, for identifying tissue which expresses a tumor-associated antigen. Antibodies may also be coupled to specific diagnostic substances for displaying cells and tissues expressing tumor-associated antigens. They may also be coupled to therapeutically useful substances. Diagnostic substances comprise, in a nonlimiting manner, barium sulfate, iocetamic acid, iopanoic acid, calcium ipodate, sodium diatrizoate, meglumine diatrizoate, metrizamide, sodium tyropanoate and radio diagnostic, including positron emitters such as fluorine-18 and carbon-11, gamma emitters such as iodine-123, technetium-99m, iodine-131 and indium-111, nuclides for nuclear magnetic resonance, such as fluorine and gadolinium. According to the invention, the term "therapeutically useful substance" means any therapeutic molecule which, as desired, is selectively guided to a cell which expresses one or more tumor-associated antigens, including anticancer agents, radioactive iodine-labeled compounds, toxins, cytostatic or cytolytic drugs, etc. Anticancer agents comprise, for example, aminoglutethimide, azathioprine, bleomycin sulfate, busulfan, carmustine, chlorambucil, cisplatin, cyclophosphamide, cyclosporine, cytarabidine, dacarbazine, dactinomycin, daunorubin, doxorubicin, taxol, etoposide, fluorouracil, interferon-α, lomustine, mercaptopurine, methotrexate, mitotane, procarbazine HCl, thioguanine, vinblastine sulfate and vincristine sulfate. Other anticancer agents are described, for example, in Goodman and Gilman, "The Pharmacological Basis of Therapeutics", 8th Edition, 1990, McGraw-Hill, Inc., in particular Chapter 52 (Antineoplastic Agents (Paul Calabresi and Bruce A. Chabner). Toxins may be proteins such as

pokeweed antiviral protein, cholera toxin, pertussis toxin, ricin, gelonin, abrin, diphtheria exotoxin or *Pseudomonas* exotoxin. Toxin residues may also be high energy-emitting radionuclides such as cobalt-60.

The term "patient" means according to the invention a human being, a nonhuman primate or another animal, in particular a mammal such as a cow, horse, pig, sheep, goat, dog, cat or a rodent such as a mouse and rat. In a particularly preferred embodiment, the patient is a human being.

According to the invention, the term "disease" refers to any pathological state in which tumor-associated antigens are expressed or abnormally expressed. "Abnormal expression" means according to the invention that expression is altered, preferably increased, compared to the state in a healthy individual. An increase in expression refers to an increase by at least 10%, in particular at least 20%, at least 50% or at least 100%. In one embodiment, the tumor-associated antigen is expressed only in tissue of a diseased individual, while expression in a healthy individual is repressed. One example of such a disease is cancer, in particular seminomas, melanomas, teratomas, gliomas, gastrointestinal cancer, colorectal cancer, pancreas cancer, ear, nose and throat (ENT) cancer, breast cancer, prostate cancer, cancer of the uterus, ovarian cancer and lung cancer.

According to the invention, a biological sample may be a tissue sample and/or a cellular sample and may be obtained in the conventional manner such as by tissue biopsy, including punch biopsy, and by taking blood, bronchial aspirate, sputum, urine, feces or other body fluids, for use in the various methods described herein.

According to the invention, the term "immunoreactive

cell" means a cell which can mature into an immune cell (such as B cell, T helper cell, or cytolytic T cell) with suitable stimulation. Immunoreactive cells comprise $CD34^+$ hematopoietic stem cells, immature and mature T cells and immature and mature B cells. If production of cytolytic or T helper cells recognizing a tumor-associated antigen is desired, the immunoreactive cell is contacted with a cell expressing a tumor-associated antigen under conditions which favor production, differentiation and/or selection of cytolytic T cells and of T helper cells. The differentiation of T cell precursors into a cytolytic T cell, when exposed to an antigen, is similar to clonal selection of the immune system.

Some therapeutic methods are based on a reaction of the immune system of a patient, which results in a lysis of antigen-presenting cells such as cancer cells which present one or more tumor-associated antigens. In this connection, for example autologous cytotoxic T lymphocytes specific for a complex of a tumor-associated antigen and an MHC molecule are administered to a patient having a cellular abnormality. The production of such cytotoxic T lymphocytes *in vitro* is known. An example of a method of differentiating T cells can be found in WO-A-9633265. Generally, a sample containing cells such as blood cells is taken from the patient and the cells are contacted with a cell which presents the complex and which can cause propagation of cytotoxic T lymphocytes (e.g. dendritic cells). The target cell may be a transfected cell such as a COS cell. These transfected cells present the desired complex on their surface and, when contacted with cytotoxic T lymphocytes, stimulate propagation of the latter. The clonally expanded autologous cytotoxic T lymphocytes are then administered to the patient.

In another method of selecting antigen-specific cytotoxic T lymphocytes, fluorogenic tetramers of MHC

class I molecule/peptide complexes are used for detecting specific clones of cytotoxic T lymphocytes (Altman et al., *Science* 274:94-96, 1996; Dunbar et al., *Curr. Biol.* 8:413-416, 1998). Soluble MHC class I molecules are folded *in vitro* in the presence of β_2 microglobulin and a peptide antigen binding to said class I molecule. The MHC/peptide complexes are purified and then labeled with biotin. Tetramers are formed by mixing the biotinylated peptide-MHC complexes with labeled avidin (e.g. phycoerythrin) in a molar ratio of 4:1. Tetramers are then contacted with cytotoxic T lymphocytes such as peripheral blood or lymph nodes. The tetramers bind to cytotoxic T lymphocytes which recognize the peptide antigen/MHC class I complex. Cells which are bound to the tetramers may be sorted by fluorescence-controlled cell sorting to isolate reactive cytotoxic T lymphocytes. The isolated cytotoxic T lymphocytes may then be propagated *in vitro*.

In a therapeutic method referred to as adoptive transfer (Greenberg, *J. Immunol.* 136(5):1917, 1986; Riddel et al., *Science* 257:238, 1992; Lynch et al., *Eur. J. Immunol.* 21:1403-1410, 1991; Kast et al., *Cell* 59:603-614, 1989), cells presenting the desired complex (e.g. dendritic cells) are combined with cytotoxic T lymphocytes of the patient to be treated, resulting in a propagation of specific cytotoxic T lymphocytes. The propagated cytotoxic T lymphocytes are then administered to a patient having a cellular anomaly characterized by particular abnormal cells presenting the specific complex. The cytotoxic T lymphocytes then lyse the abnormal cells, thereby achieving a desired therapeutic effect.

Often, of the T cell repertoire of a patient, only T cells with low affinity for a specific complex of this kind can be propagated, since those with high affinity have been extinguished due to development of tolerance.

An alternative here may be a transfer of the T cell receptor itself. For this too, cells presenting the desired complex (e.g. dendritic cells) are combined with cytotoxic T lymphocytes of healthy individuals or another species (e.g. mouse). This results in propagation of specific cytotoxic T lymphocytes with high affinity if the T lymphocytes are derived from a donor organism which had no previous contact with the specific complex. The high affinity T cell receptor of these propagated specific T lymphocytes is cloned. If the high affinity T cell receptors have been cloned from another species they can be humanized to a different extent. Such T cell receptors are then transduced via gene transfer, for example using retroviral vectors, into T cells of patients, as desired. Adoptive transfer is then carried out using these genetically altered T lymphocytes (Stanislawski et al., Nat Immunol. 2:962-70, 2001; Kessels et al., Nat Immunol. 2:957-61, 2001).

The therapeutic aspects above start out from the fact that at least some of the abnormal cells of the patient present a complex of a tumor-associated antigen and an HLA molecule. Such cells may be identified in a manner known per se. As soon as cells presenting the complex have been identified, they may be combined with a sample from the patient, which contains cytotoxic T lymphocytes. If the cytotoxic T lymphocytes lyse the cells presenting the complex, it can be assumed that a tumor-associated antigen is presented.

Adoptive transfer is not the only form of therapy which can be applied according to the invention. Cytotoxic T lymphocytes may also be generated *in vivo* in a manner known per se. One method uses nonproliferative cells expressing the complex. The cells used here will be those which usually express the complex, such as irradiated tumor cells or cells transfected with one or both genes necessary for presentation of the complex

(i.e. the antigenic peptide and the presenting HLA molecule). Various cell types may be used. Furthermore, it is possible to use vectors which carry one or both of the genes of interest. Particular preference is given to viral or bacterial vectors. For example, nucleic acids coding for a tumor-associated antigen or for a part thereof may be functionally linked to promoter and enhancer sequences which control expression of said tumor-associated antigen or a fragment thereof in particular tissues or cell types. The nucleic acid may be incorporated into an expression vector. Expression vectors may be nonmodified extrachromosomal nucleic acids, plasmids or viral genomes into which exogenous nucleic acids may be inserted. Nucleic acids coding for a tumor-associated antigen may also be inserted into a retroviral genome, thereby enabling the nucleic acid to be integrated into the genome of the target tissue or target cell. In these systems, a microorganism such as vaccinia virus, pox virus, Herpes simplex virus, retrovirus or adenovirus carries the gene of interest and de facto "infects" host cells. Another preferred form is the introduction of the tumor-associated antigen in the form of recombinant RNA which may be introduced into cells by liposomal transfer or by electroporation, for example. The resulting cells present the complex of interest and are recognized by autologous cytotoxic T lymphocytes which then propagate.

A similar effect can be achieved by combining the tumor-associated antigen or a fragment thereof with an adjuvant in order to make incorporation into antigen-presenting cells *in vivo* possible. The tumor-associated antigen or a fragment thereof may be represented as protein, as DNA (e.g. within a vector) or as RNA. The tumor-associated antigen is processed to produce a peptide partner for the HLA molecule, while a fragment thereof may be presented without the need for further processing. The latter is the case in particular, if

these can bind to HLA molecules. Preference is given to administration forms in which the complete antigen is processed *in vivo* by a dendritic cell, since this may also produce T helper cell responses which are needed for an effective immune response (Ossendorp et al., *Immunol Lett.* 74:75-9, 2000; Ossendorp et al., *J. Exp. Med.* 187:693-702, 1998). In general, it is possible to administer an effective amount of the tumor-associated antigen to a patient by intradermal injection, for example. However, injection may also be carried out intranodally into a lymph node (Maloy et al., *Proc Natl Acad Sci USA* 98:3299-303, 2001). It may also be carried out in combination with reagents which facilitate uptake into dendritic cells. Preferred tumor-associated antigens comprise those which react with allogenic cancer antisera or with T cells of many cancer patients. Of particular interest, however, are those against which no spontaneous immune responses pre-exist. Evidently, it is possible to induce against these immune responses which can lyse tumors (Keogh et al., *J. Immunol.* 167:787-96, 2001; Appella et al., *Biomed Pept Proteins Nucleic Acids* 1:177-84, 1995; Wentworth et al., *Mol Immunol.* 32:603-12, 1995).

The pharmaceutical compositions described according to the invention may also be used as vaccines for immunization. According to the invention, the terms "immunization" or "vaccination" mean an increase in or activation of an immune response to an antigen. It is possible to use animal models for testing an immunizing effect on cancer by using a tumor-associated antigen or a nucleic acid coding therefor. For example, human cancer cells may be introduced into a mouse to generate a tumor, and one or more nucleic acids coding for tumor-associated antigens may be administered. The effect on the cancer cells (for example reduction in tumor size) may be measured as a measure for the effectiveness of an immunization by the nucleic acid.

As part of the composition for an immunization, one or more tumor-associated antigens or stimulating fragments thereof are administered together with one or more adjuvants for inducing an immune response or for increasing an immune response. An adjuvant is a substance which is incorporated into the antigen or administered together with the latter and which enhances the immune response. Adjuvants may enhance the immune response by providing an antigen reservoir (extracellularly or in macrophages), activating macrophages and stimulating particular lymphocytes. Adjuvants are known and comprise in a nonlimiting way monophosphoryl lipid A (MPL, SmithKline Beecham), saponins such as QS21 (SmithKline Beecham), DQS21 (SmithKline Beecham; WO 96/33739), QS7, QS17, QS18 and QS-L1 (So et al., Mol. Cells 7:178-186, 1997), incomplete Freund's adjuvant, complete Freund's adjuvant, vitamin E, montanide, alum, CpG oligonucleotides (cf. Kreig et al., Nature 374:546-9, 1995) and various water-in-oil emulsions prepared from biologically degradable oils such as squalene and/or tocopherol. Preferably, the peptides are administered in a mixture with DQS21/MPL. The ratio of DQS21 to MPL is typically about 1:10 to 10:1, preferably about 1:5 to 5:1 and in particular about 1:1. For administration to humans, a vaccine formulation typically contains DQS21 and MPL in a range from about 1 µg to about 100 µg.

Other substances which stimulate an immune response of the patient may also be administered. It is possible, for example, to use cytokines in a vaccination, owing to their regulatory properties on lymphocytes. Such cytokines comprise, for example, interleukin-12 (IL-12) which was shown to increase the protective actions of vaccines (cf. *Science* 268:1432-1434, 1995), GM-CSF and IL-18.

There are a number of compounds which enhance an immune

response and which therefore may be used in a vaccination. Said compounds comprise costimulating molecules provided in the form of proteins or nucleic acids. Examples of such costimulating molecules are B7-1 and B7-2 (CD80 and CD86, respectively) which are expressed on dendritic cells (DC) and interact with the CD28 molecule expressed on the T cells. This interaction provides a costimulation (signal 2) for an antigen/MHC/TCR-stimulated (signal 1) T cell, thereby enhancing propagation of said T cell and the effector function. B7 also interacts with CTLA4 (CD152) on T cells, and studies involving CTLA4 and B7 ligands demonstrate that B7-CTLA4 interaction can enhance antitumor immunity and CTL propagation (Zheng, P. et al., *Proc. Natl. Acad. Sci.* USA 95(11):6284-6289 (1998)).

B7 is typically not expressed on tumor cells so that these are no effective antigen-presenting cells (APCs) for T cells. Induction of B7 expression would enable tumor cells to stimulate more effectively propagation of cytotoxic T lymphocytes and an effector function. Costimulation by a combination of B7/IL-6/IL-12 revealed induction of IFN-gamma and Th1-cytokine profile in a T cell population, resulting in further enhanced T cell activity (Gajewski et al., *J. Immunol.* 154:5637-5648 (1995)).

A complete activation of cytotoxic T lymphocytes and a complete effector function require an involvement of T helper cells via interaction between the CD40 ligand on said T helper cells and the CD40 molecule expressed by dendritic cells (Ridge et al., *Nature* 393:474 (1998), Bennett et al., *Nature* 393:478 (1998), Schönberger et al., *Nature* 393:480 (1998)). The mechanism of this costimulating signal probably relates to the increase in B7 production and associated IL-6/IL-12 production by said dendritic cells (antigen-presenting cells). CD40-CD40L interaction thus

complements the interaction of signal 1 (antigen/MHC-TCR) and signal 2 (B7-CD28).

The use of anti-CD40 antibodies for stimulating dendritic cells would be expected to directly enhance a response to tumor antigens which are usually outside the range of an inflammatory response or which are presented by nonprofessional antigen-presenting cells (tumor cells). In these situations, T helper and B7-costimulating signals are not provided. This mechanism could be used in connection with therapies based on antigen-pulsed dendritic cells.

The invention also provides for administration of nucleic acids, polypeptides or peptides. Polypeptides and peptides may be administered in a manner known per se. In one embodiment, nucleic acids are administered by *ex vivo* methods, i.e. by removing cells from a patient, genetic modification of said cells in order to incorporate a tumor-associated antigen and reintroduction of the altered cells into the patient. This generally comprises introducing a functional copy of a gene into the cells of a patient *in vitro* and reintroducing the genetically altered cells into the patient. The functional copy of the gene is under the functional control of regulatory elements which allow the gene to be expressed in the genetically altered cells. Transfection and transduction methods are known to the skilled worker. The invention also provides for administering nucleic acids *in vivo* by using vectors such as viruses and target-controlled liposomes.

In a preferred embodiment, a viral vector for administering a nucleic acid coding for a tumor-associated antigen is selected from the group consisting of adenoviruses, adeno-associated viruses, pox viruses, including vaccinia virus and attenuated pox viruses, Semliki Forest virus, retroviruses, Sindbis virus and Ty virus-like particles. Particular

preference is given to adenoviruses and retroviruses. The retroviruses are typically replication-deficient (i.e. they are incapable of generating infectious particles).

Various methods may be used in order to introduce according to the invention nucleic acids into cells *in vitro* or *in vivo*. Methods of this kind comprise transfection of nucleic acid $CaPO_4$ precipitates, transfection of nucleic acids associated with DEAE, transfection or infection with the above viruses carrying the nucleic acids of interest, liposome-mediated transfection, and the like. In particular embodiments, preference is given to directing the nucleic acid to particular cells. In such embodiments, a carrier used for administering a nucleic acid to a cell (e.g. a retrovirus or a liposome) may have a bound target control molecule. For example, a molecule such as an antibody specific for a surface membrane protein on the target cell or a ligand for a receptor on the target cell may be incorporated into or attached to the nucleic acid carrier. Preferred antibodies comprise antibodies which bind selectively a tumor-associated antigen. If administration of a nucleic acid via liposomes is desired, proteins binding to a surface membrane protein associated with endocytosis may be incorporated into the liposome formulation in order to make target control and/or uptake possible. Such proteins comprise capsid proteins or fragments thereof which are specific for a particular cell type, antibodies to proteins which are internalized, proteins addressing an intracellular site, and the like.

The therapeutic compositions of the invention may be administered in pharmaceutically compatible preparations. Such preparations may usually contain pharmaceutically compatible concentrations of salts, buffer substances, preservatives, carriers, supplementing immunity-enhancing substances such as

adjuvants, CpG and cytokines and, where appropriate, other therapeutically active compounds.

The therapeutically active compounds of the invention may be administered via any conventional route, including by injection or infusion. The administration may be carried out, for example, orally, intravenously, intraperitonealy, intramuscularly, subcutaneously or transdermally. Preferably, antibodies are therapeutically administered by way of a lung aerosol. Antisense nucleic acids are preferably administered by slow intravenous administration.

The compositions of the invention are administered in effective amounts. An "effective amount" refers to the amount which achieves a desired reaction or a desired effect alone or together with further doses. In the case of treatment of a particular disease or of a particular condition characterized by expression of one or more tumor-associated antigens, the desired reaction relates to inhibition of the course of the disease. This comprises slowing down the progress of the disease and, in particular, interrupting the progress of the disease. The desired reaction in a treatment of a disease or of a condition may also be delay of the onset or a prevention of the onset of said disease or said condition.

An effective amount of a composition of the invention will depend on the condition to be treated, the severeness of the disease, the individual parameters of the patient, including age, physiological condition, size and weight, the duration of treatment, the type of an accompanying therapy (if present), the specific route of administration and similar factors.

The pharmaceutical compositions of the invention are preferably sterile and contain an effective amount of the therapeutically active substance to generate the

desired reaction or the desired effect.

The doses administered of the compositions of the invention may depend on various parameters such as the type of administration, the condition of the patient, the desired period of administration, etc. In the case that a reaction in a patient is insufficient with an initial dose, higher doses (or effectively higher doses achieved by a different, more localized route of administration) may be used.

Generally, doses of the tumor-associated antigen of from 1 ng to 1 mg, preferably from 10 ng to 100 µg, are formulated and administered for a treatment or for generating or increasing an immune response. If the administration of nucleic acids (DNA and RNA) coding for tumor-associated antigens is desired, doses of from 1 ng to 0.1 mg are formulated and administered.

The pharmaceutical compositions of the invention are generally administered in pharmaceutically compatible amounts and in pharmaceutically compatible compositions. The term "pharmaceutically compatible" refers to a nontoxic material which does not interact with the action of the active component of the pharmaceutical composition. Preparations of this kind may usually contain salts, buffer substances, preservatives, carriers and, where appropriate, other therapeutically active compounds. When used in medicine, the salts should be pharmaceutically compatible. However, salts which are not pharmaceutically compatible may used for preparing pharmaceutically compatible salts and are included in the invention. Pharmacologically and pharmaceutically compatible salts of this kind comprise in a nonlimiting way those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, citric, formic, malonic, succinic acids, and the like. Pharmaceutically

compatible salts may also be prepared as alkali metal salts or alkaline earth metal salts, such as sodium salts, potassium salts or calcium salts.

A pharmaceutical composition of the invention may comprise a pharmaceutically compatible carrier. According to the invention, the term "pharmaceutically compatible carrier" refers to one or more compatible solid or liquid fillers, diluents or encapsulating substances, which are suitable for administration to humans. The term "carrier" refers to an organic or inorganic component, of a natural or synthetic nature, in which the active component is combined in order to facilitate application. The components of the pharmaceutical composition of the invention are usually such that no interaction occurs which substantially impairs the desired pharmaceutical efficacy.

The pharmaceutical compositions of the invention may contain suitable buffer substances such as acetic acid in a salt, citric acid in a salt, boric acid in a salt and phosphoric acid in a salt.

The pharmaceutical compositions may, where appropriate, also contain suitable preservatives such as benzalkonium chloride, chlorobutanol, parabens and thimerosal.

The pharmaceutical compositions are usually provided in a uniform dosage form and may be prepared in a manner known per se. Pharmaceutical compositions of the invention may be in the form of capsules, tablets, lozenges, suspensions, syrups, elixirs or in the form of an emulsion, for example.

Compositions suitable for parenteral administration usually comprise a sterile aqueous or nonaqueous preparation of the active compound, which is preferably isotonic to the blood of the recipient. Examples of

compatible carriers and solvents are Ringer solution and isotonic sodium chloride solution. In addition, usually sterile, fixed oils are used as solution or suspension medium.

The present invention is described in detail by the figures and examples below, which are used only for illustration purposes and are not meant to be limiting. Owing to the description and the examples, further embodiments which are likewise included in the invention are accessible to the skilled worker.

Figures:

Fig. 1. GPR35 mRNA expression in colon carcinoma biopsies

RT-PCR investigations with DNA-free RNA show GPR35 expression in most of the colon carcinoma biopsies. By contrast, there is no detectable expression in normal tissues. (1-Breast, 2-lung, 3-lymph nodes, 4-thymus, 5-colon, 6-15 colon carcinoma, 16-neg. control).

Fig. 2. Quantitative PCR analysis of GUCY2C mRNA expression in normal and tumor tissues

Real-time PCR investigation with GUCY2C-specific primers (SEQ ID NO: 22-23) shows selective mRNA expression in normal ileum, colon, and in all colon carcinoma biopsies. Distinct quanities of GUCY2C transcripts were also detected in a colon carcinoma metastasis in the liver.

Fig. 3. Identification of tumor-specific GUCY2C splice variants

PCR products from normal colon tissues and colon carcinomas were cloned, and clones from both groups were checked by restriction analysis (EcoR I) and sequenced.

Fig. 4. Selective SCGB3A expression in normal lung and

lung carcinoma

RT-PCR analysis with gene-specific SCGB3A2 primers (SEQ ID NO: 37, 38) shows cDNA amplification exclusively in normal lung (lane 8, 14-15) and in lung carcinoma biopsies (lane 16-24). (1-Liver-N, 2-PBMC-N, 3-lymph node-N, 4-stomach-N, 5-testis-N, 6-breast-N, 7-kidney-N, 8-lung-N, 9-thymus-N, 10-ovary-N, 11-adrenal-N, 12-spleen-N, 14-15-lung-N, 16-24-lung carcinoma, 25-negative control).

Fig. 5. Claudin-18A2.1 expression in stomach, esophagus, stomach carcinoma and pancreatic carcinoma

RT-PCR analysis with claudin-18A2.1-specific primers (SEQ ID NO: 39, 40) showed according to the invention pronounced claudin-18A2.1 expression in 8/10 stomach carcinoma biopsies and in 3/6 pancreatic carcinoma biopsies. Distinct expression was also detected in stomach and normal esophageal tissue. In contrast thereto, no expression was detected in the ovary and in ovarian carcinoma.

Fig. 6. SLC13A1 expression in the kidney and renal cell carcinoma

RT-PCR analysis with SLC13A1-specific primers (SEQ ID NO: 49, 50) showed expression in 7/8 renal cell carcinoma samples. Otherwise, transcripts within normal tissues were detected exclusively in the kidney. (1-2-kidney, 3-10-renal cell carcinoma, 11-breast, 12-lung, 13-liver, 14-colon, 15-lymph nodes, 16-spleen, 17-esophagus, 18-thymus, 19-thyroid, 20-PBMCs, 21-ovary, 22-testis).

Fig. 7. CLCA1 expression in colon, colon carcinoma and stomach carcinoma

RT-PCR investigations with CLCA1-specific primers (SEQ ID NO: 67, 68) confirmed selective expression in the colon and showed high expression in (3/7) investigated colon carcinoma and (1/3) investigated stomach carcinoma samples. The other normal tissues

(NT) showed no or only very weak expression.

Fig. 8. FLJ21477 expression in the colon and colon carcinoma

RT-PCR investigations with FLJ21477-specific primers (SEQ ID NO: 69, 70) showed selective expression in the colon and additionally various levels of expression in (7/12) investigated colon carcinoma samples. The other normal tissues (NT) showed no expression.

Fig. 9. FLJ20694 expression in the colon and colon carcinoma

RT-PCR investigations with FLJ20694-specific primers (SEQ ID NO: 71, 72) showed selective expression in the colon and additionally various levels of expression in (5/9) investigated colon carcinoma samples. The other normal tissues (NT) showed no expression.

Fig. 10. von Ebner expression in stomach, lung and lung carcinoma

RT-PCR investigations with von Ebner-specific primers (SEQ ID NO: 73, 74) showed selective expression in the stomach, in the lung and in (5/10) investigated lung carcinoma samples. The other normal tissues (NT) showed no expression.

Fig. 11. Plunc expression in thymus, lung and lung carcinoma

RT-PCR investigations with Plunc-specific primers (SEQ ID NO: 75, 76) showed selective expression in the thymus, in the lung and in (6/10) investigated lung carcinoma samples. The other normal tissues showed no expression.

Fig. 12. SLC26A9 expression in lung, lung carcinoma and thyroid

RT-PCR investigations with SLC26A9-specific primers (SEQ ID NO: 77, 78) showed selective expression in the lung and in all (13/13) investigated lung carcinoma

samples. The other normal tissues (NT) showed no expression with the exception of the thyroid.

Fig. 13. THC1005163 expression in stomach, ovary, lung and lung carcinoma

RT-PCR investigations with a THC1005163-specific primer (SEQ ID NO: 79) and a nonspecific oligo dT tag primer showed expression in stomach, ovary, lung and in (5/9) lung carcinoma biopsies. The other normal tissues (NT) showed no expression.

Fig. 14. LOC134288 expression in kidney and renal cell carcinoma

RT-PCR investigations with LOC134288-specific primers (SEQ ID NO: 80, 81) showed selective expression in the kidney and in (5/8) investigated renal cell carcinoma biopsies.

Fig. 15. THC943866 expression in kidney and renal cell carcinoma

RT-PCR investigations with THC943866-specific primers (SEQ ID NO: 82, 83) showed selective expression in the kidney and in (4/8) investigated renal cell carcinoma biopsies.

Fig. 16. FLJ21458 expression in colon and colon carcinoma

RT-PCR investigations with FLJ21458-specific primers (SEQ ID NO: 86, 87) showed selective expression in the colon and in (7/10) investigated colon carcinoma biopsies. (1-2-colon, 3-liver, 4-PBMCs, 5-spleen, 6-prostate, 7-kidney, 8-ovary, 9-skin, 10-ileum, 11-lung, 12-testis, 13-22 colon carcinoma, 23-neg. control).

Examples:

Material and methods

The terms "*in silico*", "electronic" and "virtual cloning" refer solely to the utilization of methods based on databases, which may also be used to simulate laboratory experimental processes.

Unless expressly defined otherwise, all other terms and expressions are used so as to be understood by the skilled worker. The techniques and methods mentioned are carried out in a manner known per se and are described, for example, in Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edition (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. All methods including the use of kits and reagents are carried out according to the manufacturers' information.

Datamining-based strategy for determining new tumor-associated genes

Two *in silico* strategies, namely GenBank keyword search and the cDNAxProfiler, were combined (fig. 1). Utilizing the NCBI ENTREZ Search and Retrieval System (http://www.ncbi.nlm.nih.gov/Entrez), a GenBank search was carried out for candidate genes annotated as being specifically expressed in specific tissues (Wheeler et al., *Nucleic Acids Research* 28:10-14, 2000). Carrying out queries with keywords such as "colon-specific gene", "stomach-specific gene" or "kidney-specific gene", candidate genes (GOI, genes of interest) were extracted from the databases. The search was restricted to part of the total information of these databases by using the limits "homo sapiens", for the organism, and "mRNA", for the type of molecule.

The list of the GOI found was curated by determining different names for the same sequence and eliminating such redundancies.

All candidate genes obtained by the keyword search were in turn studied with respect to their tissue distribution by the "electronic Northern" (eNorthen) method. The eNorthern is based on aligning the sequence of a GOI with an EST (expressed sequence tag) database (Adams et al., *Science* 252:1651, 1991) (http://www.ncbi.nlm.nih.gov/BLAST). The tissue origin of each EST which is found to be homologous to the inserted GOI can be determined and in this way the sum of all ESTs produces a preliminary assessment of the tissue distribution of the GOI. Further studies were carried out only with those GOI which had no homologies to EST from non organ-specific normal tissues. This evaluation also took into account that the public domain contains wrongly annotated cDNA libraries (Scheurle et al., *Cancer Res.* 60:4037-4043, 2000) (www.fau.edu/cmbb/publications/cancergenes6.htm).

The second datamining method utilized was the **cDNA xProfiler** of the NCBI Cancer Genome Anatomy Project (http://cgap.nci.nih.gov/Tissues/xProfiler) (Hillier et al., *Genome Research* 6:807-828, 1996; Pennisi, *Science* 276:1023-1024, 1997). This allows pools of transcriptomes deposited in databases to be related to one another by logical operators. We have defined a pool A to which all expression libraries prepared for example from colon were assigned, excluding mixed libraries. All cDNA libraries prepared from normal tissues other than colon were assigned to pool B. Generally, all cDNA libraries were utilized independently of underlying preparation methods, but only those with a size > 1000 were admitted. Pool B was digitally subtracted from pool A by means of the BUT NOT operator. The set of GOI found in this manner was also subjected to eNorthern studies and validated by a literature research.

This combined datamining includes all of the about 13 000 full-length genes in the public domain and predicts out of these genes having potential organ-specific expression.

All other genes were first evaluated in normal tissues by means of specific RT-PCR. All GOI which had proved to be expressed in non-organ specific normal tissues had to be regarded as false-positives and were excluded from further studies. The remaining ones were studied in a large panel of a wide variety of tumor tissues. The antigens depicted below proved here to be activated in tumor cells.

RNA extraction, preparation of poly-d(T) primed cDNA and RT-PCR analysis

Total RNA was extracted from native tissue material by using guanidium isothiocyanate as chaotropic agent (Chomczynski & Sacchi, *Anal. Biochem.* 162:156-9, 1987). After extraction with acidic phenol and precipitation with isopropanol, said RNA was dissolved in DEPC-treated water.

First strand cDNA synthesis from 2-4 µg of total RNA was carried out in a 20 µl reaction mixture by means of Superscript II (Invitrogen), according to the manufacturer's information. The primer used was a dT(18) oligonucleotide. Integrity and quality of the cDNA were checked by amplification of p53 in a 30 cycle PCR (sense CGTGAGCGCTTCGAGATGTTCCG, antisense CCTAACCAGCTGCCCAACTGTAG, hybridization temperature 67°C).

An archive of first strand cDNAs was prepared from a number of normal tissues and tumor entities. For expression studies, 0.5 µl of these cDNAs was amplified in a 30 µl reaction mixture, using GOI-specific primers (see below) and 1 U of HotStarTaq DNA polymerase (Qiagen). Each reaction mixture contained 0.3 mM dNTPs, 0.3 µM of each primer and 3 µl of 10 × reaction buffer. The primers were selected so as to be located in two different exons, and elimination of the interference by contaminating genomic DNA as the reason for false-positive results was confirmed by testing nonreverse-transcribed DNA as template. After 15 minutes at 95°C

to activate the HotStarTaq DNA polymerase, 35 cycles of PCR were carried out (1 min at 94°C, 1 min at the particular hybridization temperature, 2 min at 72°C and final elongation at 72°C for 6 min).

20 µl of this reaction were fractionated and analyzed on an ethidium bromide-stained agarose gel.

The following primers were used for expression analysis of the corresponding antigens at the hybridization temperature indicated.

GPR35 (65°C)

Sense: 5'-AGGTACATGAGCATCAGCCTG-3'

Antisense: 5'-GCAGCAGTTGGCATCTGAGAG-3'

GUCY2C (62°C)

Sense: 5´-GCAATAGACATTGCCAAGATG-3´

Antisense: 5´-AACGCTGTTGATTCTCCACAG-3´

SCGB3A2 (66°C)

Sense: 5'-CAGCCTTTGTAGTTACTCTGC-3'

Antisense: 5'-TGTCACACCAAGTGTGATAGC-3'

Claudin18A2.1 (68°C)

Sense: 5´-GGTTCGTGGTTTCACTGATTGGGATTGC-3´

Antisense: 5´-CGGCTTTGTAGTTGGTTTCTTCTGGTG-3´

SLC13A1 (64°C)

Sense: 5'-CAGATGGTTGTGAGGAGTCTG-3´

Antisense: 5'-CCAGCTTTAACCATGTCAATG-3´

CLCA1 (62°C)

Sense: 5'-ACACGAATGGTAGATACAGTG-3´

Antisense: 5'-ATACTTGTGAGCTGTTCCATG-3´

FLJ21477 (68°C)

Sense: 5'- ACTGTTACCTTGCATGGACTG-3´

Antisense: 5'- CAATGAGAACACATGGACATG-3´

FLJ20694 (64°C)

Sense: 5'- CCATGAAAGCTCCATGTCTA-3´

Antisense: 5'- AGAGATGGCACATATTCTGTC

Ebner (70°C)

Sense: 5′-ATCGGCTGAAGTCAAGCATCG-3′

Antisense: 5′-TGGTCAGTGAGGACTCAGCTG-3′

Plunc (55°C)

Sense: 5′-TTTCTCTGCTTGATGCACTTG-3′

Antisense: 5′-GTGAGCACTGGGAAGCAGCTC-3′

SLC26A9 (67°C)

Sense: 5′-GGCAAATGCTAGAGACGTGA-3′

Antisense: 5′-AGGTGTCCTTCAGCTGCCAAG-3′

THC1005163 (60°C)

Sense: 5′- GTTAAGTGCTCTCTGGATTTG-3′

LOC134288 (64°C)

Sense: 5′-ATCCTGATTGCTGTGTGCAAG-3′

Antisense: 5′-CTCTTCTAGCTGGTCAACATC-3′

THC943866 (59°C)

Sense: 5′-CCAGCAACAACTTACGTGGTC-3′

Antisense: 5′-CCTTTATTCACCCAATCACTC-3′

FLJ21458 (62°C)

Sense: 5′-ATTCATGGTTCCAGCAGGGAC-3'

Antisense: 5′-GGGAGACAAAGTCACGTACTC-3'

Preparation of random hexamer-primed cDNA and quantitative real-time PCR

The principle of quantitative real time PCR using the ABI PRISM Sequence Detection System (PE Biosystems, USA) utilizes the 5′-3′ exonuclease activity of Taq DNA polymerase for direct and specific detection of PCR products via release of fluorescence reporter dyes. In addition to sense and antisense primers, the PCR employs a doubly fluorescently labeled probe (TaqMan probe) which hybridizes to a sequence of the PCR product. The probe is labeled 5′ with a reporter dye (e.g. FAM) and 3′ with a quencher dye (e.g. TAMRA). If the probe is intact, the spatial proximity of reporter to quencher suppresses the emission of reporter fluorescence. If the probe hybridizes to the PCR product during the PCR, said probe is cleaved by the

5'-3' exonuclease activity of Taq DNA polymerase and suppression of the reporter fluorescence is removed. The increase in reporter fluorescence as a consequence of the amplification of the target, is measured after each PCR cycle and utilized for quantification. Expression of the target gene is quantified absolutely or relative to expression of a control gene with constant expression in the tissues to be studied. The reactions were carried out in duplex mixtures and determined in duplicate. cDNA was synthesized using the High Capacity cDNA Archive Kit (PE Biosystems, USA) and hexamer primers according to the manufacturer's information. In each case 5 µl of the diluted cDNA were used for the PCR in a total volume of 25 µl: sense primer (GGTGTCACTTCTGTGCCTTCCT) 300 nM; antisense primer (CGGCACCAGTTCCAACAATAG) 300 nM; TaqMan probe (CAAAGGTTCTCCAAATGT) 250 nM; sense primer 18s RNA 50 nM; antisense primer 18s RNA 50 nM; 18s RNA sample 250 nM; 12.5 µl TaqMan Universal PCR Master Mix; initial denaturation 95°C (10 min); 95°C (15 sec); 60°C (1 min); 40 cycles.

Cloning and sequence analysis

Cloning of full-lengths and gene fragments took place by conventional methods. To ascertain the sequence, corresponding antigenes were amplified using the proofreading polymerase pfu (Stratagene). After completion of the PCR, adenosine was ligated by means of HotStarTaq DNA polymerase to the ends of the amplicon in order to clone the fragments in accordance with the manufacturer's instructions into the TOPO-TA vector. The sequencing was carried out by a commercial service. The sequences were analysed using conventional prediction programs and algorithms.

Example 1: Identification of GPR35 as diagnostic and therapeutic cancer target

GPR35 (SEQ ID NO:1) and its translation product (SEQ ID NO:9) have been described as putative G

protein-coupled receptor. The sequence is published in Genbank under accession No. AF089087. This transcript codes for a protein of 309 amino acids with a molecular weight of 34 kDa. It was predicted that GPR35 belongs to the superfamily of G protein-coupled receptors with 7 transmembrane domains (O'Dowd et al., *Genomics* 47:310-13, 1998). The gene is located on the long arm of the 2nd chromosome and comprises a single exon.

According to the invention, a gene-specific primer pair (SEQ ID NO:20, 21) for GPR35 was used in RT-PCR analyses to amplify cDNA in the colon and in colon carcinoma (13/26). By contrast, no significant expression is detectable in other normal tissues. This is contradictory to published data according to which GPR35 transcripts were detected ubiquitarily in normal tissues (O'Dowd et al., *Genomics* 47:310-13, 1998). Because of the particular fact that GPR35 consists of a single exon, genomic DNA impurities cannot be detected with intron-spanning primers. In order to preclude genomic contamination of the RNA samples, therefore, all RNAs were treated with DNAse. GPR35 transcripts were detected according to the invention only in the colon, and in colon carcinomas using DNA-free RNA.

Tab. 1 GPR35 expression in normal tissues

Normal tissue	**Expression**
Brain	nd
Cerebellum	nd
Myocardium	nd
Skeletal muscle	nd
Heart muscle	nd
Stomach	nd
Colon (large intestine)	++
Pancreas	nd
Kidney	-
Liver	-
Testis (testicle)	nd
Thymus	-
Mamma (breast)	-
Ovary	-
Uterus	nd
Skin	-
Lung	-
Thyroid	nd
Lymph nodes	-
Spleen	-
PBMC	-
Adrenal	-
Esophagus	-
Small intestine	-
Prostate	-

(nd = not determined)

The selective and high expression of GPR35 transcripts in normal colonic tissue and in colon carcinoma biopsies (fig. 1) can be utilized according to the invention for molecular diagnostic methods such as RT-PCR for detecting disseminating tumor cells in the serum and bone marrow and for detecting metastases in other tissues.

The 4 extracellular domains of GPR35 can be used according to the invention as target structures of monoclonal antibodies. These antibodies bind specifically to the cell surface of tumor cells and can be used both for diagnostic and for therapeutic methods.

In addition, the sequences coding for proteins can be used according to the invention as vaccine (RNA, DNA, peptide, protein) for inducing tumor-specific immune responses (T-cell and B-cell-mediated immune responses).

In addition, according to the cellular function of the GPR35 molecule, substances, in particular small molecules, may be developed according to the invention which modulate the function of GPR35 on tumor cells.

Example 2: Identification of GUCY2C splice variants as diagnostic and therapeutic cancer targets

Guanylate cyclase 2C (SEQ ID NO:2) its translation product (SEQ ID NO:11) - a type I transmembrane protein - belongs to the family of natriuretic peptide receptors. The sequence is published in Genbank under the accession number NM_004963. Binding of the peptides guanylin and uroguanylin, respectively, or else heat-stable enterotoxins (STa) increases the intracellular cGMP concentration, thus inducing signal transduction processes inside the cell.

Recent investigations indicate that expression of GUCY2C also extends to extraintestinal regions such as, for example, primary and metastatic adenocarcinomas of the stomach and of the esophagus (Park et al., *Cancer*

Epidemiol Biomarkers Prev. 11: 739-44, 2002). A splice variant of GUCYC which is found both in normal and transformed tissue of the intestine comprises a 142 bp deletion in exon 1, thus preventing translation of a GUCY2C-like product (Pearlman et al., *Dig. Dis. Sci.* 45:298-05, 2000). The only splice variant described to date leads to no translation product. According to the invention, the aim of our investigations was to identify tumor-associated splice variants for GUCY2C which can be utilized both for diagnosis and for therapy.

RT-PCR investigations with a GUCY2C-specific primer pair (SEQ ID NO:22, 23) show pronounced expression of GUCY2C transcripts in normal colon, and weak expression in stomach, liver, testis, ovary, thymus, spleen, and lung (tab. 2). Marked GUCY2C transcript levels were detected in colon carcinoma and stomach carcinoma (tab. 2). These results were specified by a quantitative PCR analysis and showed pronounced GUCY2C expression in normal colon, ileum, and in almost all colon carcinoma samples investigated (fig. 2).

The following primer pairs were used to detect splice variants in colonic tissue and colon carcinoma tissue: GUCY2C-118s/GUCY2C-498as (SEQ ID NO:24, 29); GUCY2C-621s/GUCY2C-1140as (SEQ ID NO:25, 30); GUCY2C-1450s/GUCY2C-1790as (SEQ ID NO:26, 31); GUCY2C-1993s/GUCY2C-2366as (SEQ ID NO:27, 32); GUCY2C-2717s/GUCY2C-3200as (SEQ ID NO:28, 33); GUCY2C-118s/GUCY2C-1140as (SEQ ID NO:24, 30); GUCY2C-621s/GUCY2C-1790as (SEQ ID NO:25, 31); GUCY2C-1450s/GUCY2C-2366as (SEQ ID NO:26, 32); GUCY2C-1993s/GUCY2C-3200as (SEQ ID NO:27, 33).

On investigation of splice variants in colon carcinoma tissue, three previously unknown forms were identified according to the invention.

a) A deletion of exon 3 (SEQ ID NO:3) which leads to a variant of GUCY2C which is only 111 amino acids long and in which the asparagine at

position 111 is replaced by a proline.

b) Secondly, a deletion of exon 6 (SEQ ID NO:4) which results in an expression product 258 amino acids long. This would generate a C-terminal neoepitope comprising 13 amino acids.

c) Finally, a variant in which the nucleotides at positions 1606-1614, and the corresponding amino acids L(536), L(537) and Q(538), were deleted (SEQ ID NO:5).

Table 2: GUC2C expression in normal and tumor tissues

Normal tissues	Expression
Brain	
Cerebellum	
Myocardium	
Skeletal muscle	
Heart muscle	
Stomach	+
Colon (large intestine)	+++
Pancreas	
Kidney	-
Liver	+
Testis (testicle)	+
Thymus	+
Mamma (breast)	-
Ovary	+
Uterus	
Skin	
Lung	+
Thyroid	
Lymph nodes	-
Spleen	+
PBMC	-

Tumor type	Expression
Colon carcinoma	+++
Pancreatic carcinoma	-
Esophageal carcinoma	
Stomach carcinoma	+++
Bronchial carcinoma	-
Mammary carcinoma	-
Ovarian carcinoma	
Endometrial carci	
ENT tumors	
Renal cell carcinoma	
Prostate carcinoma	

The splice variants according to the invention with deletions respectively in exon 3 and exon 6, respectively, (SEQ ID NO:3, 4) are distinguished in particular by the translation products (SEQ ID NO:12, 13) having no transmembrane domain. The result in the case of exon 6 deletion is a C-terminal neoepitope of 13 amino acids which shows no homology whatsoever with previously known proteins. This neoepitope is thus predestined to be a target structure for immunotherapy. The splice variant of the invention with base deletions at positions 1606-1614 (SEQ ID NO:5) and its translation product (SEQ ID NO:14) likewise comprises a neoepitope, which, however, is located C-terminal to the transmembrane domain and thus, due to its intracellular location is protected from direct access by antibodies.

Example 3: Identification of SCGB3A2 as diagnostic and therapeutic cancer target

SCGB3A2 (SEQ ID NO:6) and its translation product (SEQ ID NO:15) belongs to the secretoglobin gene family. The sequence is published in GenBank under accession number NM_054023. SCGB3A2 (UGRP1) is a homodimeric secretory protein with a size of 17 kDa, which is expressed exclusively in the lung and in the tracheae (Niimi et al., *Am J Hum Genet* 70:718-25, 2002).

RT PCR investigations with a primer pair (SEQ ID NO:37, 38) confirmed selective expression in normal lung tissue and, according to the invention, prominent expression in the majority of the lung carcinoma biopsies investigated (fig. 4).

The investigations showed that SCGB3A2 is strongly and frequently expressed in bronchial carcinomas. Since all the other normal tissues, apart from lung and trachea, show no expression, the genetic product is suitable according to the invention as target for diagnosis and therapy.

The selective and high expression of SCGB3A2 in normal lung tissue and in lung carcinoma biopsies can be used according to the invention for molecular diagnostic methods such as RT-PCR for detecting disseminating tumor cells in blood and bone marrow, sputum, bronchial aspirate or lavage and for detecting metastases in other tissues, e.g. in local lymph nodes.

Example 4: Identification of claudin-18A2.1 as diagnostic and therapeutic cancer target

The claudin-18 gene codes for a surface membrane molecule having a tissue specific expression in lung and stomach. Niimi and colleagues (*Mol. Cell. Biol.* 21:7380-90, 2001) were able to show that for human claudin-18, two splice variants exist which are expressed selectively in lung tissue (claudin-18A1.1) and in stomach tissue (claudin-18A2.1), respectively. It was investigated whether claudin-18A2.1 (SEQ ID NO:7) and its translation product (SEQ ID NO:16) can be used as markers for tumors of the upper gastrointestinal tract, in particular stomach carcinoma and pancreatic carcinoma. Oligonucleotides (SEQ ID NO: 39, 40) which enable specific amplification of this splice variant were used for this purpose.

Table 3. Expression of claudin-18A2.1 in normal and tumor tissues

Normal tissue	Expression
Brain	
Cerebellum	
Myocardium	
Skeletal muscle	
Heart muscle	
Stomach	+++
Colon (large intestine)	
Pancreas	++
Kidney	-
Liver	-
Testis (testicle)	
Thymus	
Mamma (breast)	-
Ovary	-
Uterus	
Skin	
Lung	-
Thyroid	
Lymph nodes	
Spleen	
PBMC	-
Esophagus	+++

Tumor type	Expression
Colon carcinoma	
Pancreatic carcinoma	++
Esophageal carcinoma	
Gastric carcinoma	+++
Bronchial carcinoma	
Breast carcinoma	
Ovarian carcinoma	-
Endometrial carcinoma	
ENT tumors	
Renal cell carcinoma	
Prostate carcinoma	

It was shown according to the invention that 8/10 gastric carcinomas and half of the tested pancreatic carcinomas showed strong expression of this splice variant (fig. 5). By contrast, expression is not detectable in other tissues. In particular, there is no expression in lung, liver, blood, lymph nodes, breast tissue and kidney tissue (tab. 3). This splice variant thus represents according to the invention a highly specific molecular marker for the metastasis of tumors of the upper gastrointestinal tract. This molecular marker can be used according to the invention for both detecting tumor cells and therapeutic targeting of tumors of the upper gastrointestinal tract. Detection of the tumors is possible according to the invention with oligonucleotides specific for the claudin18A2.1 splice variant (SEQ ID NO:39, 40). Particularly suitable oligonucleotides are primer pairs of which at least one binds under stringent conditions to a segment of the transcript which is 180 base pairs long and is specific for this splice variant (SEQ ID NO:8). Tumor cells may also be detected according to the invention using antibodies which recognize a specific epitope encoded by claudin18A2.1. For the production of the antibodies, peptides specific for this splice variant can be used for immunization according to the invention. For the immunization, in particular the amino acids 1-47 (SEQ ID NO: 19) are useful which distinctly differ in the epitope compared to the lung specific splice variant of this gene. The specific expression in tumors of the upper gastrointestinal tract also makes claudin18A2.1 according to the invention a therapeutic target for these tumors, in particular by immunotherapeutic methods, such as vaccine, monoclonal antibodies and adoptive transfer of antigen-specific T lymphocytes, respectively. In this respect, the amino acids 1-47 (SEQ ID NO: 19) also represent particularly good epitopes. According to the invention, in particular the following peptides DQWSTQDLYN (SEQ ID NO: 17), NNPVTAVFNYQ (SEQ ID NO: 18)

or homologous peptides are suitable for immunization to prepare monoclonal antibodies which are therapeutically used. These epitopes are regions of the molecule which are located extracellularly and can be targeted according to the invention by therapeutically administered antibodies.

Example 5: Identification of SLC13A1 as diagnostic and therapeutic cancer target

SLC13A1 belongs to the family of sodium sulfate cotransporters. The human gene is, in contrast to the mouse homolog of this gene, selectively expressed in the kidney (Lee et al., *Genomics* 70:354-63). SLC13A1 codes for a protein of 595 amino acids and comprises 13 putative transmembrane domains. Alternative splicing results in 4 different transcripts (SEQ ID NO:41-44) and its corresponding translation products (SEQ ID NO:45-48). It was investigated whether SLC13A1 can be used as marker for kidney tumors. Oligonucleotides (SEQ ID NO:49, 50) which enable specific amplification of SLC13A1 were used for this purpose.

Tab. 4. Expression of SLC13A1 in normal and tumor tissues

Normal tissue	Expression
Brain	nd
Cerebellum	nd
Myocardium	nd
Skeletal muscle	nd
Heart muscle	nd
Stomach	nd
Colon (large intestine)	nd
Pancreas	nd
Kidney	-
Liver	-
Testis (testicle)	-
Thymus	-
Mamma (breast)	-
Ovary	-
Uterus	nd
Skin	nd
Lung	-
Thyroid	-
Lymph nodes	-
Spleen	-
PBMC	-
Sigmoid	-
Esophagus	-

Tumor type	Expression
Colon carcinoma	nd
Pancreatic carcinoma	nd
Esophageal carcinoma	nd
Gastric carcinoma	nd
Bronchial carcinoma	nd
Breast carcinoma	nd
Ovarian carcinoma	nd
Endometrial carcinoma	nd
ENT tumors	nd
Renal cell carcinoma	7/8
Prostate carcinoma	nd

RT-PCR investigations with an SLC13A1-specific primer pair (SEQ ID NO:49, 50) confirmed selective expression in the kidney, and showed according to the invention a high expression in virtually all (7/8) investigated renal cell carcinoma biopsies (tab. 4, fig. 6).
The pronounced expression and high incidence of SLC13A1 in renal cell carcinomas make this protein according to the invention a highly interesting diagnostic and therapeutic marker. This includes according to the invention the detection of disseminating tumor cells in serum, bone marrow, urine, and detection of metastases in other organs by means of RT-PCR. It is additionally possible to use the extracellular domains of SLC13A1 according to the invention as target structure for immunodiagnosis and therapy by means of monoclonal antibodies. SLC13A1 can moreover be employed according to the invention as vaccine (RNA, DNA, protein, peptides) for inducing tumor-specific immune responses (T and B cell-mediated immune responses). This includes according to the invention also the development of so-called small compounds which modulate the biological activity of SLC13A1 and can be employed for the therapy of renal tumors.

Example 6: Identification of CLCA1 as diagnostic and therapeutic cancer target

CLCA1 (SEQ ID NO:51) and its translation product (SEQ ID NO:60) belongs to the family of Ca^{++}-activated Cl^- channels. The sequence is published in Genbank under the accession No. NM_001285. CLCA1 is exclusively expressed in the intestinal crypt epithelium and in the goblet cells (Gruber et al., *Genomics* 54:200-14, 1998). It was investigated whether CLCA1 can be used as marker for colonic and gastric carcinoma. Oligonucleotides (SEQ ID NO:67, 68) which enable specific amplification of SLC13A1 were used for this purpose. RT-PCR investigations with this primer set confirmed selective expression in the colon, and showed according to the

invention high expression in (3/7) investigated colonic and (1/3) investigated gastric carcinoma samples (fig. 7). The other normal tissues showed no or only very weak expression.

Example 7: Identification of FLJ21477 as diagnostic and therapeutic cancer target

FLJ21477 (SEQ ID NO:52) and its predicted translation product (SEQ ID NO:61) was published as hypothetical protein in Genbank under the accession No. NM_025153. RT-PCR investigations with FLJ21477-specific primers (SEQ ID NO:69, 70) showed selective expression according to the invention in the colon, and additionally various levels of expression in (7/12) investigated colonic carcinoma samples (fig. 8). The other normal tissues showed no expression.

Example 8: Identification of FLJ20694 as diagnostic and therapeutic cancer target

FLJ21477 (SEQ ID NO:53) and its predicted translation product (SEQ ID NO:62) was published as hypothetical protein in Genbank under accession No. NM_017928. RT-PCR investigations with FLJ20694-specific primers (SEQ ID NO:71, 72) showed selective expression according to the invention in the colon, and additionally various levels of expression in (5/9) investigated colonic carcinoma samples (fig. 9). The other normal tissues showed no expression.

Example 9: Identification of von Ebner's protein as diagnostic and therapeutic cancer target

von Ebner's protein (SEQ ID NO:54) and its translation product (SEQ ID NO:63) was published as Plunc-related protein of the upper airways and of the nasopharyngeal epithelium in Genbank under the accession No. AF364078. It was investigated according to the invention whether

von Ebner's protein can be used as marker of lung carcinoma. Oligonucleotides (SEQ ID NO:73, 74) which enable specific amplification of SLC13A1 were used for this purpose. RT-PCR investigations with this primer set showed selective expression in the lung and, according to the invention, in (5/10) investigated lung carcinoma samples (fig. 10). In the group of normal tissues there was also expression in the stomach. The other normal tissues showed no expression.

Example 10: Identification of Plunc as diagnostic and therapeutic cancer target

Plunc (SEQ ID NO:55) and its translation product (SEQ ID NO:64) was published in Genbank under the accession No. NM_016583. Human Plunc codes for a protein of 256 amino acids and shows 72% homology with the murine Plunc protein (Bingle and Bingle, *Biochim Biophys Acta* 1493:363-7, 2000). Expression of Plunc is confined to the trachea, the upper airways, nasopharyngeal epithelium and salivary gland.
It was investigated according to the invention whether Plunc can be used as marker of lung carcinoma. For this purpose, we used oligonucleotides (SEQ ID NO:75, 76) which enable specific amplification of Plunc.
RT-PCR investigations with this primer set showed selective expression in the thymus, in the lung and in (6/10) investigated lung carcinoma samples (fig. 11). The other normal tissues showed no expression.

Example 11: Identification of SLC26A9 as diagnostic and therapeutic cancer target

SLC26A9 (SEQ ID NO:56) and its translation product (SEQ ID NO:65) was published in Genbank under the accession No. NM_134325. SLC26A9 belongs to the family of anion exchangers. Expression of SLC26A9 is confined to the bronchiolar and alveolar epithelium of the lung (Lohi et al., J Biol Chem 277:14246-54, 2002).

It was investigated whether SLC26A9 can be used as marker of lung carcinoma. Oligonucleotides (SEQ ID NO:77, 78) which enable specific amplification of SLC26A9 were used for this purpose. RT-PCR investigations with SLC26A9-specific primers (SEQ ID NO:77, 78) showed selective expression in the lung and, according to the invention, in all (13/13) investigated lung carcinoma samples (fig. 12). The other normal tissues showed no expression, with the exception of the thyroid.

Example 12: Identification of THC1005163 as diagnostic and therapeutic cancer target

THC1005163 (SEQ ID NO:57) is a gene fragment from the TIGR gene index. The gene is defined only in the 3′ region, while an ORF is lacking. RT-PCR investigations took place with a THC1005163-specific primer (SEQ ID NO:79) and an oligo dT_{18} primer which had a specific tag of 21 specific bases at the 5′ end. This tag was examined using database search programs for homology with known sequences. This specific primer was initially employed in the cDNA synthesis in order to preclude genomic DNA contaminations. RT-PCR investigations with this primer set showed expression in the stomach, ovary, lung and, according to the invention, in (5/9) lung carcinoma biopsies (fig. 13). The other normal tissues showed no expression.

Example 13: Identification of LOC134288 as diagnostic and therapeutic cancer target

LOC134288 (SEQ ID NO:58) and its predicted translation product (SEQ ID NO:66) was published in Genbank under accession No. XM_059703.
It was investigated according to the invention whether LOC134288 can be used as marker of renal cell carcinoma. Oligonucleotides (SEQ ID NO:80, 81) which enable specific amplification of LOC134288 were used

for this purpose. RT-PCR investigations showed selective expression in the kidney and in (5/8) investigated renal cell carcinoma biopsies (fig. 14).

Example 14: Identification of THC943866 as diagnostic and therapeutic cancer target

THC 943866 (SEQ ID NO:59) is a gene fragment from the TIGR gene index. The gene is defined only in the 3' region, while an ORF is lacking. Thus, up to now no translation product could be predicted.
It was investigated whether THC943866 can be used as marker of renal cell carcinoma. Oligonucleotides (SEQ ID NO:82, 83) which enable specific amplification of THC943866 were used for this purpose.
RT-PCR investigations with THC943866-specific primers (SEQ ID NO:82, 83) showed selective expression in the kidney and in (4/8) investigated renal cell carcinoma biopsies (fig. 15).

Example 15: Identification of FLJ21458 as diagnostic and therapeutic cancer target

FLJ21458 (SEQ ID NO:84) and its predicted translation product (SEQ ID NO:85) was published in Genbank under the accession No. NM_034850.
It was investigated whether FLJ21458 can be used as marker of colonic carcinoma. Oligonucleotides (SEQ ID NO:86, 87) which enable specific amplification of FLJ21458 were used for this purpose.
RT-PCR investigations with FLJ21458-specific primers (SEQ ID NO:86, 87) showed selective expression in colon and in (7/10) investigated colonic carcinoma biopsies (fig. 16, tab. 5). Bioinformatic investigations showed that the protein encoded by FLJ21458 represents a cell surface molecule and has an immunoglobulin supermolecule domain. Selective expression of this surface molecule makes it a good target for developing diagnostic methods for the detection of tumor cells and

therapeutic methods for the elimination of tumor cells.

Tab. 5 FLJ21458 expression in normal and tumor tissues

Normal tissue	Expression
Brain	nd
Cerebellum	nd
Myocardium	nd
Skeletal muscle	nd
Heart muscle	nd
Stomach	nd
Colon (large intestine)	++
Pancreas	nd
Kidney	-
Liver	-
Testis (testicle)	-
Thymus	nd
Mamma (breast)	nd
Ovary	-
Uterus	nd
Skin	-
Lung	-
Thyroid (thyroid gland)	nd
Lymph nodes	nd
Spleen	-
PBMC	-
Adrenal	nd
Esophagus	nd
Small intestine	-
Prostate	-

Tumor type	Expression
Colonic carcinoma	7/10
Pancreatic carcinoma	nd
Esophageal carcinoma	nd
Gastric carcinoma	nd
Bronchial carcinoma	nd
Breast carcinoma	nd
Ovarian carcinoma	nd
Endometrial carcinoma	nd
ENT tumors	nd
Renal cell carcinoma	nd
Prostate carcinoma	nd

Claims

1. A pharmaceutical composition, comprising an agent which inhibits expression or activity of a tumor-associated antigen, said tumor-associated antigen having a sequence encoded by a nucleic acid which is selected from the group consisting of:
(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,
(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,
(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and
(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

2. A pharmaceutical composition, comprising an agent with tumor-inhibiting activity, which is selective for cells expressing or abnormally expressing a tumor-associated antigen, said tumor-associated antigen having a sequence encoded by a nucleic acid which is selected from the group consisting of:
(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,
(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,
(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and
(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

3. The pharmaceutical composition as claimed in claim 2, in which the agent causes induction of cell death, reduction in cell growth, damage to the

cell membrane or secretion of cytokines.

4. The pharmaceutical composition as claimed in claim 1 or 2, in which the agent is an antisense nucleic acid which hybridizes selectively with the nucleic acid coding for the tumor-associated antigen.

5. The pharmaceutical composition as claimed in claim 1 or 2, in which the agent is an antibody which binds selectively to the tumor-associated antigen.

6. The pharmaceutical composition as claimed in claim 2, in which the agent is a complement-activating antibody which binds selectively to the tumor-associated antigen.

7. A pharmaceutical composition, comprising an agent which, when administered, selectively increases the amount of complexes between an HLA molecule and a tumor-associated antigen or a part thereof, said tumor-associated antigen having a sequence encoded by a nucleic acid which is selected from the group consisting of:
(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,
(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,
(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and
(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

8. The pharmaceutical composition as claimed in claim 7, in which the agent comprises one or more components selected from the group consisting of:
(i) the tumor-associated antigen or a part thereof,

(ii) a nucleic acid which codes for the tumor-associated antigen or a part thereof,
(iii) a host cell which expresses the tumor-associated antigen or a part thereof, and
(iv) isolated complexes between the tumor-associated antigen or a part thereof and an HLA molecule.

9. The pharmaceutical composition as claimed in claim 1, 2 or 7, in which the agent comprises two or more agents which in each case selectively inhibit expression or activity of different tumor-associated antigens, which are in each case selective for cells expressing different tumor-associated antigens or which increase the amount of complexes between HLA molecules and different tumor-associated antigens or parts thereof, with at least one of said tumor-associated antigens having a sequence encoded by a nucleic acid which is selected from the group consisting of:
(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,
(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,
(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and
(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

10. A pharmaceutical composition, comprising one or more components selected from the group consisting of:
(i) a tumor-associated antigen or a part thereof,
(ii) a nucleic acid which codes for a tumor-associated antigen or a part thereof,
(iii) an antibody which binds to a tumor-associated antigen or a part thereof,

(iv) an antisense nucleic acid which hybridizes specifically with a nucleic acid coding for a tumor-associated antigen,

(v) a host cell which expresses a tumor-associated antigen or a part thereof, and

(vi) isolated complexes between a tumor-associated antigen or a part thereof and an HLA molecule,

said tumor-associated antigen having a sequence encoded by a nucleic acid which is selected from the group consisting of:

(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,

(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,

(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and

(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

11. The pharmaceutical composition as claimed in claim 8 or 10, in which the nucleic acid of (ii) is present in an expression vector.

12. The pharmaceutical composition as claimed in claim 8 or 10, in which the nucleic acid of (ii) is functionally linked to a promoter.

13. The pharmaceutical composition as claimed in claim 8 or 10, in which the host cell secretes the tumor-associated antigen or the part thereof.

14. The pharmaceutical composition as claimed in claim 8 or 10, in which the host cell additionally expresses an HLA molecule which binds to the tumor-associated antigen or the part thereof.

15. The pharmaceutical composition as claimed in claim

14, in which the host cell expresses the HLA molecule and/or the tumor-associated antigen or the part thereof in a recombinant manner.

16. The pharmaceutical composition as claimed in claim 14, in which the host cell expresses the HLA molecule endogenously.

17. The pharmaceutical composition as claimed in claim 8, 10, 14 or 16, in which the host cell is an antigen-presenting cell.

18. The pharmaceutical composition as claimed in claim 17, in which the antigen-presenting cell is a dendritic cell or a macrophage.

19. The pharmaceutical composition as claimed in any of claims 8, 10 and 13-18, in which the host cell is nonproliferative.

20. The pharmaceutical composition as claimed in claim 5 or 10, in which the antibody is a monoclonal antibody.

21. The pharmaceutical composition as claimed in claim 5 or 10, in which the antibody is a chimeric or humanized antibody.

22. The pharmaceutical composition as claimed in claim 5 or 10, in which the antibody is a fragment of a natural antibody.

23. The pharmaceutical composition as claimed in claim 5 or 10, in which the antibody is coupled to a therapeutic or diagnostic agent.

24. The pharmaceutical composition as claimed in claim 4 or 10, in which the antisense nucleic acid comprises a sequence of 6-50 contiguous

nucleotides of the nucleic acid coding for the tumor-associated antigen.

25. The pharmaceutical composition as claimed in any of claims 8 and 10-13, in which the tumor-associated antigen or the part thereof, provided by said pharmaceutical composition, binds to MHC molecules on the surface of cells which express an abnormal amount of said tumor-associated antigen or of a part thereof.

26. The pharmaceutical composition as claimed in claim 25, in which the binding causes a cytolytic reaction and/or induces cytokine release.

27. The pharmaceutical composition as claimed in any of claims 1-26, further comprising a pharmaceutically acceptable carrier and/or an adjuvant.

28. The pharmaceutical composition as claimed in claim 27, in which the adjuvant is saponin, GM-CSF, CpG, cytokine or a chemokine.

29. The pharmaceutical composition as claimed in any of claims 1-28, which may be used for the treatment of a disease characterized by expression or abnormal expression of a tumor-associated antigen.

30. The pharmaceutical composition as claimed in claim 29, in which the disease is cancer.

31. The pharmaceutical composition as claimed 29, in which the disease is a lung tumor, a breast tumor, a prostate tumor, a melanoma, a colon tumor, a gastric tumor, a pancreatic tumor, an ENT tumor, a renal cell carcinoma or a cervical carcinoma, a colon carcinoma or a mammary carcinoma.

32. The pharmaceutical composition as claimed in any of claims 1-31, in which the tumor-associated antigen comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-19, 45-48, 60-66, 85, a part or derivative thereof.

33. A method of diagnosing a disease characterized by expression or abnormal expression of a tumor-associated antigen, which method comprises
(i) detection of a nucleic acid which codes for the tumor-associated antigen or of a part thereof, and/or
(ii) detection of the tumor-associated antigen or of a part thereof, and/or
(iii) detection of an antibody to the tumor-associated antigen or of a part thereof and/or
(iv) detection of cytotoxic or T helper lymphocytes which are specific to the tumor-associated antigen or to a part thereof in a biological sample isolated from a patient, with said tumor-associated antigen having a sequence encoded by a nucleic acid which is selected from the group consisting of:
(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,
(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,
(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and
(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

34. The method as claimed in claim 33, in which the detection comprises
(i) contacting the biological sample with an agent which binds specifically to the nucleic acid

coding for the tumor-associated antigen or to the part thereof, to the tumor-associated antigen or the part thereof, to the antibody or to the cytotoxic or T helper lymphocytes, and

(ii) detecting the formation of a complex between the agent and the nucleic acid or the part thereof, the tumor-associated antigen or the part thereof, the antibody or the cytotoxic or T helper lymphocytes.

35. The method as claimed in claim 33 or 34, in which the detection is compared to detection in a comparable normal biological sample.

36. The method as claimed in any of claims 33-35, in which the disease is characterized by expression or abnormal expression of two or more different tumor-associated antigens and in which detection comprises detection of two or more nucleic acids coding for said two or more different tumor-associated antigens or of parts thereof, detection of said two or more different tumor-associated antigens or of parts thereof, detection of two or more antibodies binding to said two or more different tumor-associated antigens or to parts thereof or detection of two or more cytotoxic or T helper lymphocytes specific for said two or more different tumor-associated antigens.

37. The method as claimed in any of claims 33-36, in which the nucleic acid or the part thereof is detected using a polynucleotide probe which hybridizes specifically to said nucleic acid or to said part thereof.

38. The method as claimed in claim 37, in which the polynucleotide probe comprises a sequence of 6-50 contiguous nucleotides of the nucleic acid coding for the tumor-associated antigen.

39. The method as claimed in any of claims 33-36, in which the nucleic acid or the part thereof is detected by selectively amplifying said nucleic acid or said part thereof.

40. The method as claimed in any of claims 33-36, in which the tumor-associated antigen to be detected or the part thereof are in a complex with an MHC molecule.

41. The method as claimed in claim 40, in which the MHC molecule is an HLA molecule.

42. The method as claimed in any of claims 33-36 and 40-41, in which the tumor-associated antigen or the part thereof is detected using an antibody binding specifically to said tumor-associated antigen or to said part thereof.

43. The method as claimed in any of claims 33-36, in which the antibody is detected using a protein or peptide binding specifically to said antibody.

44. A method for determining regression, course or onset of a disease characterized by expression or abnormal expression of a tumor-associated antigen, which method comprises monitoring a sample from a patient who has said disease or is suspected of falling ill with said disease, with respect to one or more parameters selected from the group consisting of:

(i) the amount of nucleic acid which codes for the tumor-associated antigen or of a part thereof,

(ii) the amount of the tumor-associated antigen or of a part thereof,

(iii) the amount of antibodies which bind to the tumor-associated antigen or to a part thereof, and

(iv) the amount of cytolytic or cytokine-releasing

T cells which are specific for a complex between the tumor-associated antigen or a part thereof and an MHC molecule, said tumor-associated antigen having a sequence encoded by a nucleic acid which is selected from the group consisting of:

(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,

(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,

(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and

(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

45. The method as claimed in claim 44, which comprises determining the parameter(s) in a first sample at a first point in time and in a further sample at a second point in time and in which the course of the disease is determined by comparing the two samples.

46. The method as claimed in claim 44 or 45, in which the disease is characterized by expression or abnormal expression of two or more different tumor-associated antigens and in which monitoring comprises monitoring

(i) the amount of two or more nucleic acids which code for said two or more different tumor-associated antigens or of parts thereof,

(ii) the amount of said two or more different tumor-associated antigens or of parts thereof,

(iii) the amount of two or more antibodies which bind to said two or more different tumor-associated antigens or to parts thereof, and/or

(iv) the amount of two or more cytolytic or cytokine-releasing T cells which are specific for complexes between said two or more different

tumor-associated antigens or of parts thereof and MHC molecules.

47. The method as claimed in any of claims 44-46, in which the amount of the nucleic acid or of the part thereof is monitored using a polynucleotide probe which hybridizes specifically to said nucleic acid or said part thereof.

48. The method as claimed in claim 47, in which the polynucleotide probe comprises a sequence of 6-50 contiguous nucleotides of the nucleic acid coding for the tumor-associated antigen.

49. The method as claimed in any of claims 44-46, in which the amount of the nucleic acid or of the part thereof is monitored by selectively amplifying said nucleic acid or said part thereof.

50. The method as claimed in any of claims 44-46, in which the amount of the tumor-associated antigen or of the part thereof is monitored using an antibody binding specifically to said tumor-associated antigen or said part thereof.

51. The method as claimed in any of claims 44-46, in which the amount of antibodies is monitored using a protein or peptide binding specifically to the antibody.

52. The method as claimed in any of claims 44-46, in which the amount of cytolytic or cytokine-releasing T cells is monitored using a cell presenting the complex between the tumor-associated antigen or the part thereof and an MHC molecule.

53. The method as claimed in any of claims 37-38, 42-43, 47-48 and 50-52, in which the

polynucleotide probe, the antibody, the protein or peptide or the cell is labeled in a detectable manner.

54. The method as claimed in claim 53, in which the detectable marker is a radioactive marker or an enzymic marker.

55. The method as claimed in any of claims 33-54, in which the sample comprises body fluid and/or body tissue.

56. A method of treating a disease characterized by expression or abnormal expression of a tumor-associated antigen, which method comprises administration of a pharmaceutical composition as claimed in any of claims 1-32, said tumor-associated antigen having a sequence encoded by a nucleic acid which is selected from the group consisting of:

(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,

(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,

(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and

(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

57. A method of treating, diagnosing or monitoring a disease characterized by expression or abnormal expression of a tumor-associated antigen, which method comprises administering an antibody binding to said tumor-associated antigen or to a part thereof and coupled to a therapeutic or diagnostic agent, said tumor-associated antigen having a sequence encoded by a nucleic acid which is

selected from the group consisting of:

(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,

(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,

(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and

(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

58. The method as claimed in claim 42, 50 or 57, in which the antibody is a monoclonal antibody.

59. The method as claimed in claim 42, 50 or 57, in which the antibody is a chimeric or humanized antibody.

60. The method as claimed in claim 42, 50 or 57, in which the antibody is a fragment of a natural antibody.

61. A method of treating a patient having a disease characterized by expression or abnormal expression of a tumor-associated antigen, which method comprises:

(i) removing a sample containing immunoreactive cells from said patient,

(ii) contacting said sample with a host cell expressing said tumor-associated antigen or a part thereof, under conditions which favor production of cytolytic or cytokine-releasing T cells against said tumor-associated antigen or a part thereof, and

(iii) introducing the cytolytic or cytokine-releasing T cells into the patient in an amount suitable for lysing cells expressing the tumor-associated antigen or a part thereof, said tumor-

associated antigen having a sequence encoded by a nucleic acid which is selected from the group consisting of:

(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,

(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,

(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and

(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

62. The method as claimed in claim 61, in which the host cell recombinantly expresses an HLA molecule binding to the tumor-associated antigen or to a part thereof.

63. The method as claimed in claim 62, in which the host cell endogenously expresses an HLA molecule binding to the tumor-associated antigen or to a part thereof.

64. A method of treating a patient having a disease characterized by expression or abnormal expression of a tumor-associated antigen, which method comprises:

(i) identifying a nucleic acid which is expressed by cells associated with said disease, said nucleic acid being selected from the group consisting of:

(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,

(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,

(c) a nucleic acid which is degenerate with

respect to the nucleic acid of (a) or (b), and
(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c),
(ii) transfecting a host cell with said nucleic acid or a part thereof,
(iii) culturing the transfected host cell for expression of said nucleic acid, and
(iv) introducing the host cells or an extract thereof into the patient in an amount suitable for increasing the immune response to the patient's cells associated with the disease.

65. The method as claimed in claim 64, which further comprises identifying an MHC molecule presenting the tumor-associated antigen or a part thereof, with the host cell expressing the identified MHC molecule and presenting the tumor-associated antigen or a part thereof.

66. The method as claimed in claim 64 or 65, in which the immune response comprises a B cell response or a T cell response.

67. The method as claimed in claim 66, in which the immune response is a T cell response comprising production of cytolytic or cytokine-releasing T cells which are specific for the host cells presenting the tumor-associated antigen or a part thereof or specific for cells of the patient which express the tumor-associated antigen or a part thereof.

68. The method as claimed in any of claims 61-67, in which the host cells are nonproliferative.

69. A method of treating a disease characterized by expression or abnormal expression of a tumor-associated antigen, which method comprises:
(i) identifying cells from the patient which

express abnormal amounts of the tumor-associated antigen,

(ii) isolating a sample of said cells,

(iii) culturing said cells, and

(iv) introducing said cells into the patient in an amount suitable for triggering an immune response to the cells, said tumor-associated antigen having a sequence encoded by a nucleic acid which is selected from the group consisting of:

(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,

(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,

(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and

(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

70. The method as claimed in any of claims 33-69, in which the disease is cancer.

71. A method of inhibiting the development of cancer in a patient, which method comprises administering an effective amount of a pharmaceutical composition as claimed in any of claims 1-32.

72. The method as claimed in any of claims 33-71, in which the tumor-associated antigen comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-19, 45-48, 60-66, 85, a part or derivative thereof.

73. A nucleic acid, selected from the group consisting of:

(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ

ID NOs: 3-5, a part or derivative thereof,
(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,
(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and
(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

74. A nucleic acid, which codes for a protein or polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-14, a part or derivative thereof.

75. A recombinant DNA or RNA molecule, which comprises a nucleic acid as claimed in claim 73 or 74.

76. The recombinant DNA molecule as claimed in claim 75, which is a vector.

77. The recombinant DNA molecule as claimed in claim 76, in which the vector is a viral vector or a bacteriophage.

78. The recombinant DNA molecule as claimed in any of claims 75-77, which further comprises expression control sequences controlling expression of the nucleic acid.

79. The recombinant DNA molecule as claimed in claim 78, in which the expression control sequences are homologous or heterologous to the nucleic acid.

80. A host cell, which comprises a nucleic acid as claimed in claim 73 or 74 or a recombinant DNA molecule as claimed in any of claims 75-79.

81. The host cell as claimed in claim 80, which further comprises a nucleic acid coding for an HLA molecule.

82. A protein or polypeptide, which is encoded by a nucleic acid as claimed in claim 73.

83. A protein or polypeptide, which comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 12-14, a part or derivative thereof.

84. An immunogenic fragment of the protein or polypeptide as claimed in claim 82 or 83.

85. A fragment of the protein or polypeptide as claimed in claim 82 or 83, which binds to human HLA receptor or human antibody.

86. An agent, which binds specifically to a protein or polypeptide or to a part thereof, said protein or polypeptide being encoded by a nucleic acid selected from the group consisting of:
(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,
(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,
(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and
(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

87. The agent as claimed in claim 86, in which the protein or polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-19, 45-48, 60-66, 85, a part or derivative thereof.

88. The agent as claimed in claim 86 or 87, which is an antibody.

89. The agent as claimed in claim 88, in which the antibody is a monoclonal, chimeric or humanized antibody or a fragment of an antibody.

90. An antibody, which binds selectively to a complex of:
(i) a protein or polypeptide or a part thereof and
(ii) an MHC molecule to which said protein or polypeptide or said part thereof binds, with said antibody not binding to (i) or (ii) alone and said protein or polypeptide being encoded by a nucleic acid selected from the group consisting of:
(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,
(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,
(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and
(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

91. The antibody as claimed in claim 90, in which the protein or polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 9-19, 45-48, 60-66, 85, a part or derivative thereof.

92. The antibody as claimed in claim 90 or 91, which is a monoclonal, chimeric or humanized antibody or a fragment of an antibody.

93. A conjugate between an agent as claimed in any of claims 86-89 or an antibody as claimed in any of claims 90-92 and a therapeutic or diagnostic agent.

94. The conjugate as claimed in claim 93, in which the therapeutic or diagnostic agent is a toxin.

95. A kit for detecting expression or abnormal expression of a tumor-associated antigen, which kit comprises agents for detection
(i) of the nucleic acid which codes for the tumor-associated antigen or of a part thereof,
(ii) of the tumor-associated antigen or of a part thereof,
(iii) of antibodies which bind to the tumor-associated antigen or to a part thereof, and/or
(iv) of T cells which are specific for a complex between the tumor-associated antigen or a part thereof and an MHC molecule, said tumor-associated antigen having a sequence encoded by a nucleic acid which is selected from the group consisting of:
(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84, a part or derivative thereof,
(b) a nucleic acid which hybridizes with the nucleic acid of (a) under stringent conditions,
(c) a nucleic acid which is degenerate with respect to the nucleic acid of (a) or (b), and
(d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c).

96. The kit as claimed in claim 95, in which the agents for detection of the nucleic acid which codes for the tumor-associated antigen or of a part thereof are nucleic acid molecules for selective amplification of said nucleic acid.

97. The kit as claimed in claim 96, in which the nucleic acid molecules for selective amplification of the nucleic acid comprise a sequence of 6-50

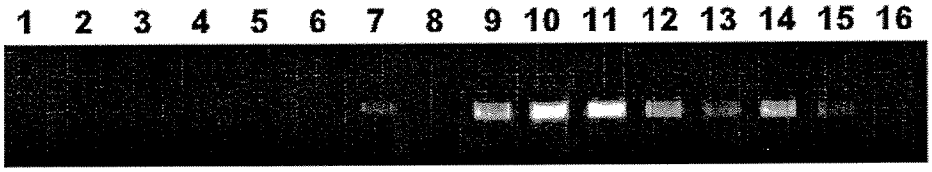
contiguous nucleotides of the nucleic acid which codes for the tumor-associated antigen.

98. A recombinant DNA molecule, comprising a promoter region which is derived from a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-8, 41-44, 51-59, 84.

Abstract

According to the invention, genetic products expressed in association with tumors and the nucleic acids coding therefor were identified. The invention relates to the therapy and diagnosis of diseases in which these genetic products are aberrantly expressed in association with tumors. In addition, the invention relates to proteins, polypeptides and peptides which are expressed in association with tumors, and to the nucleic acids coding for said polypeptides, peptides and proteins.

Fig. 1



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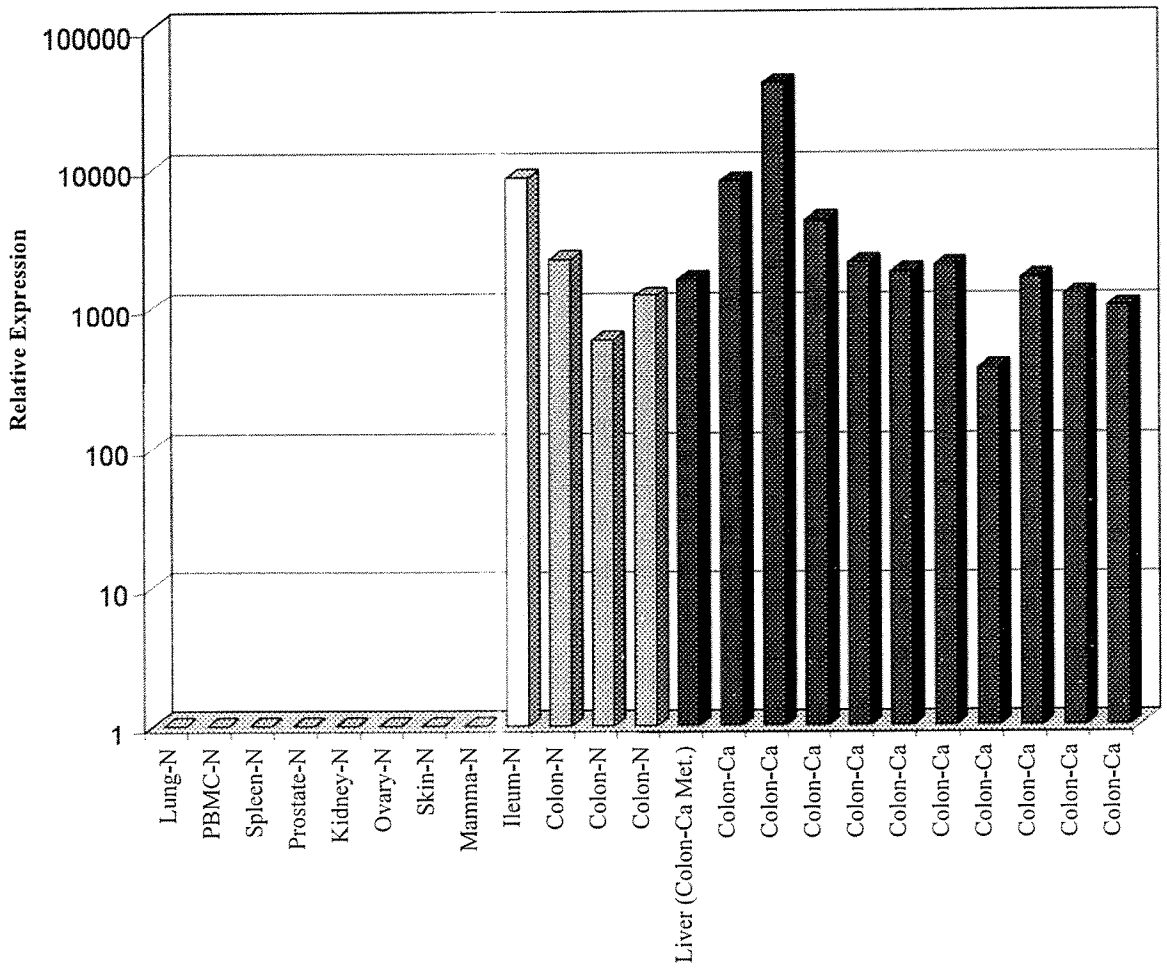
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Mamma-N
Ileum-N
Colon-N
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Colon-N
Liver (Colon-Ca Met.)
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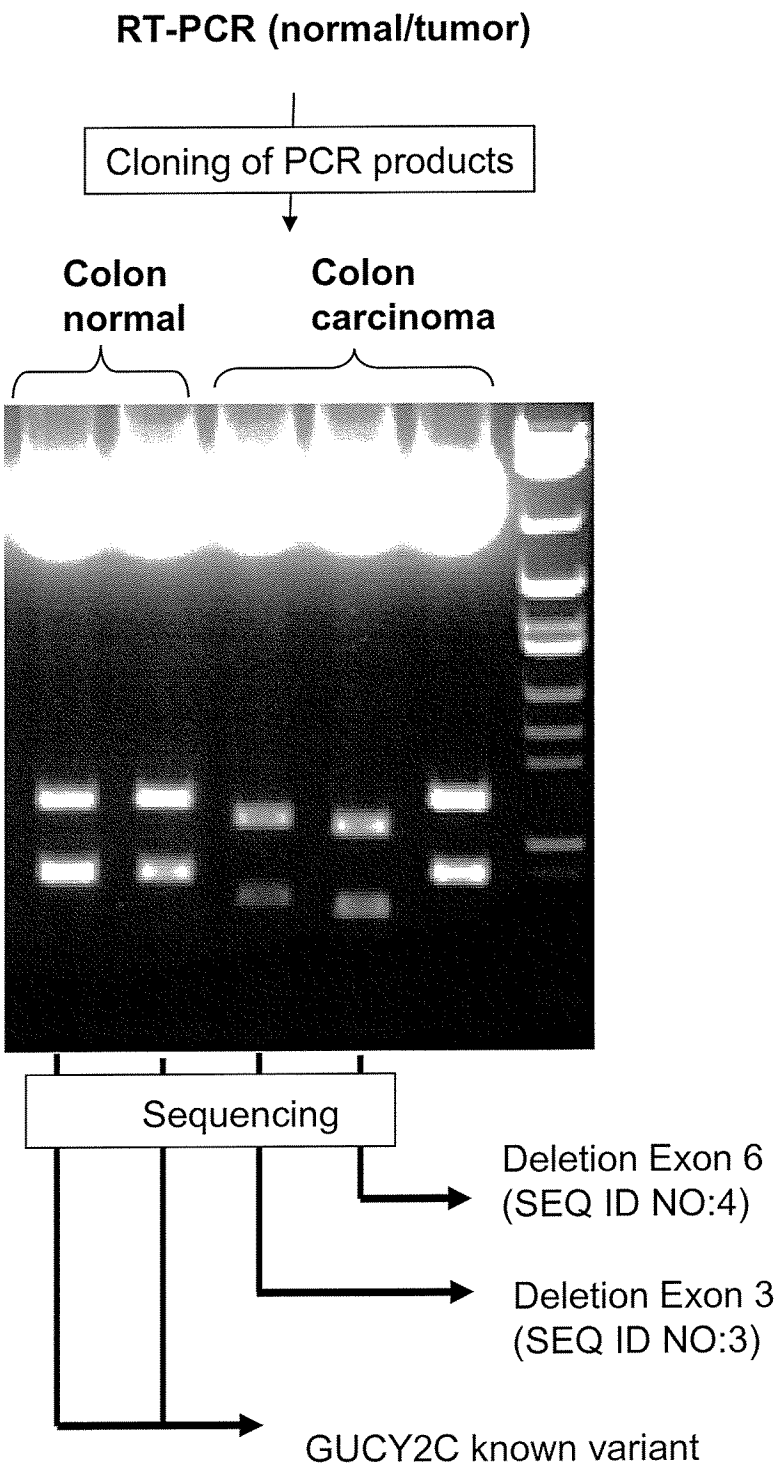
Fig. 3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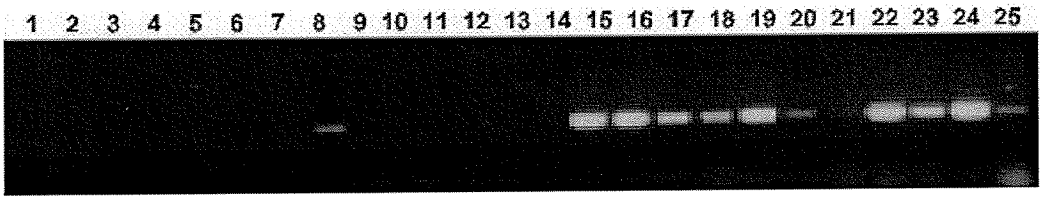

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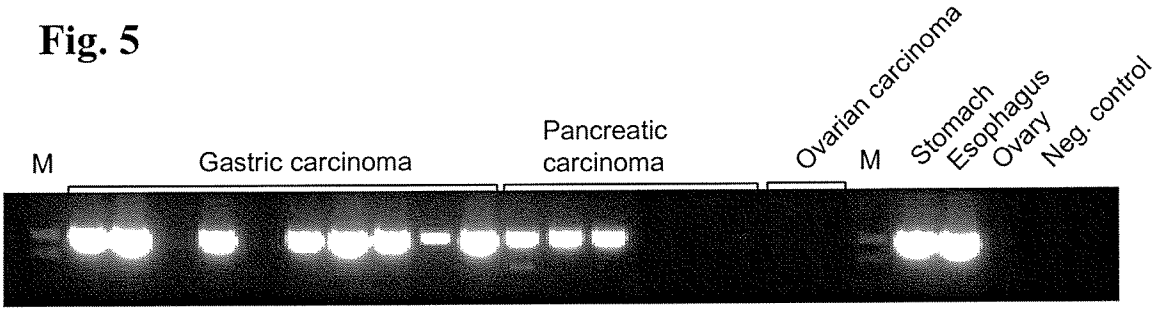
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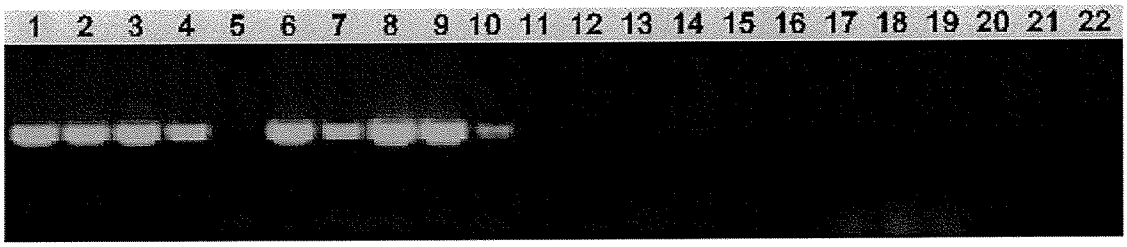
Esophagus
Ovary
Neg. control

Fig. 6



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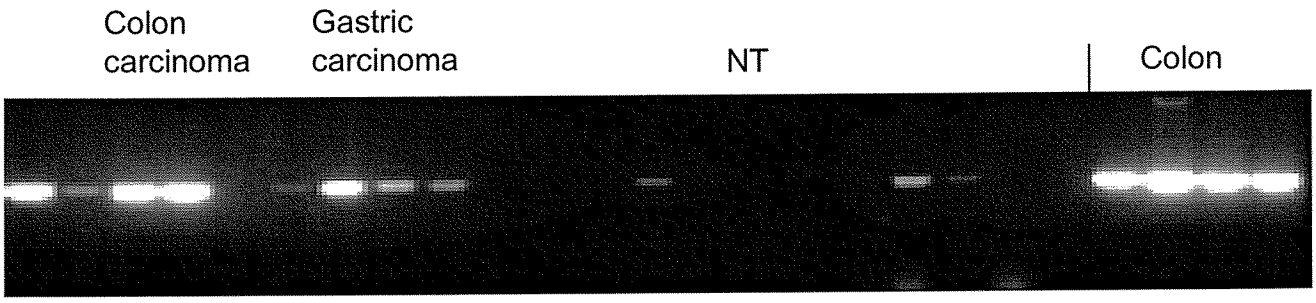

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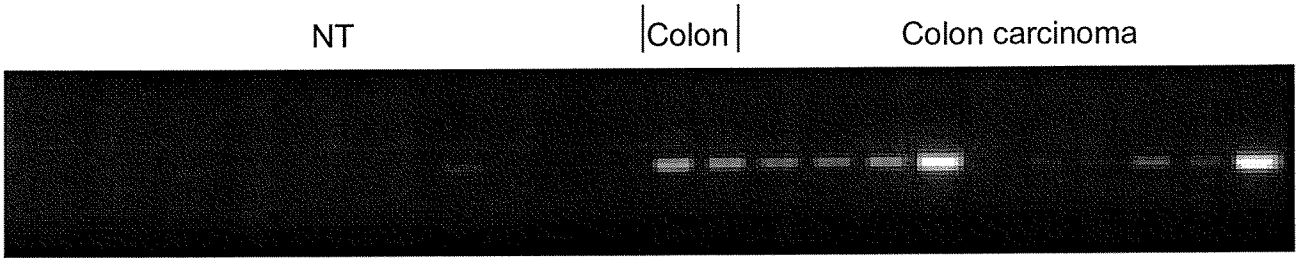

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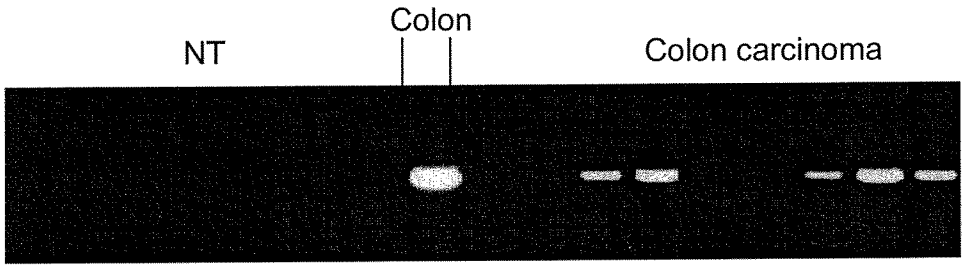


Fig. 10

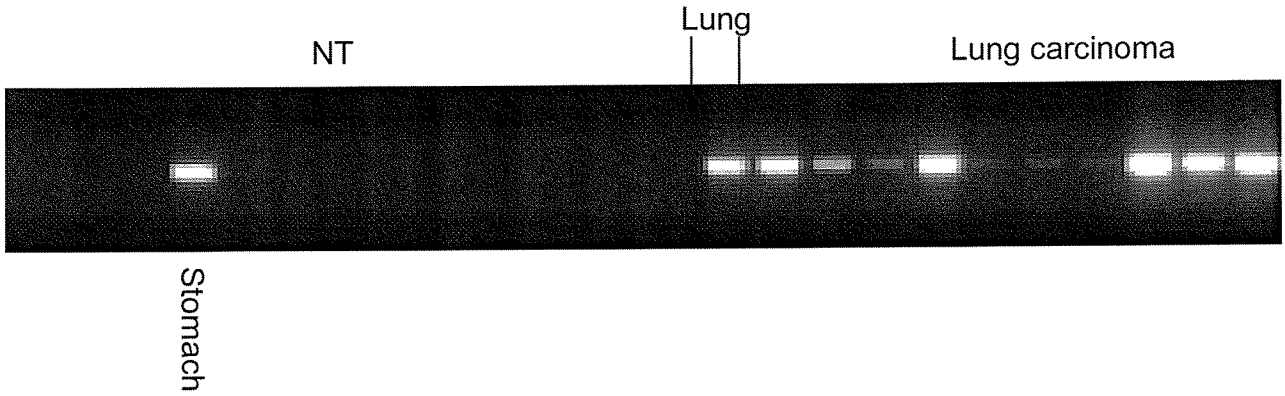


Fig. 11

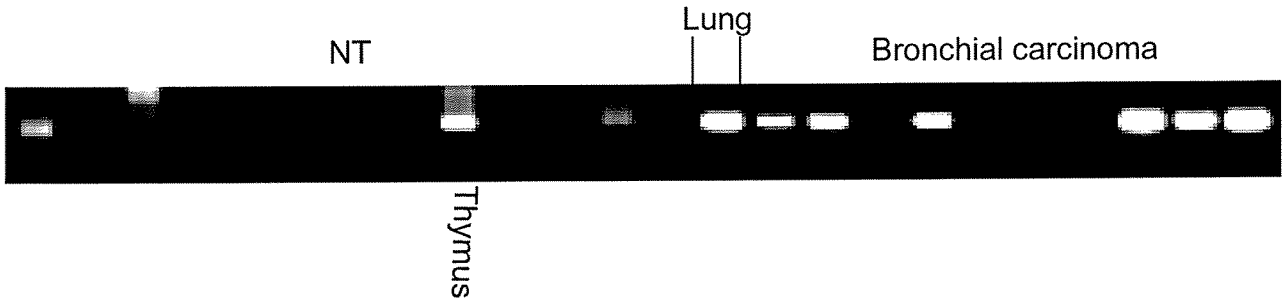


Fig. 12

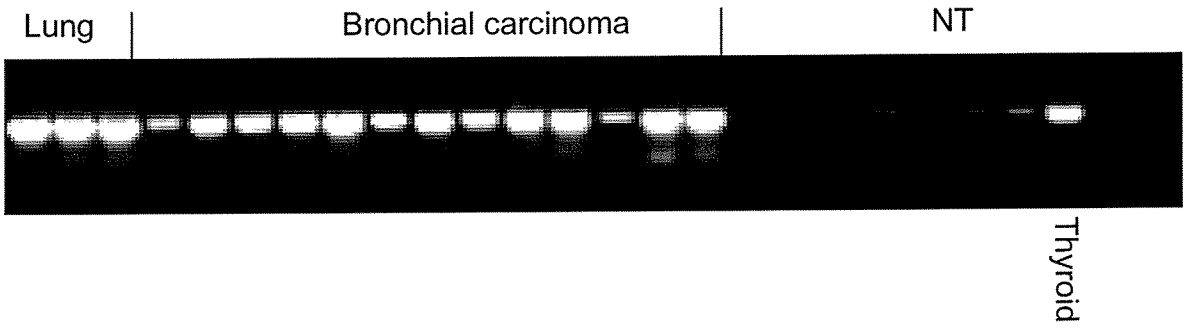


Fig. 13

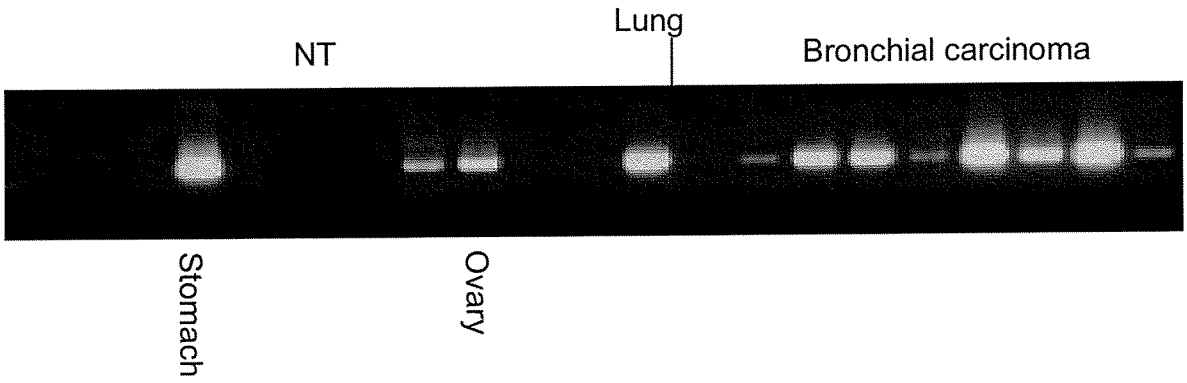


Fig. 14

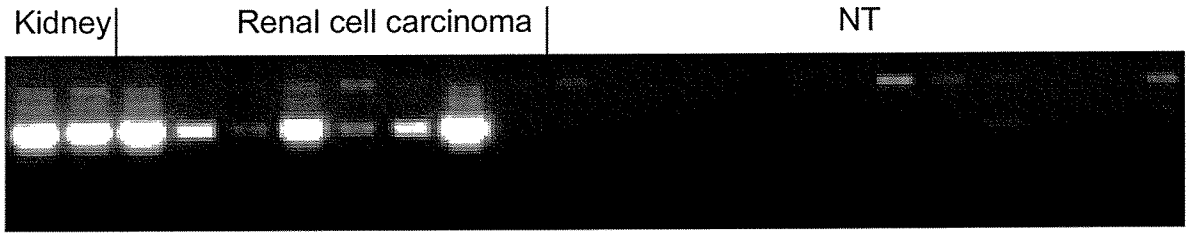


Fig. 15

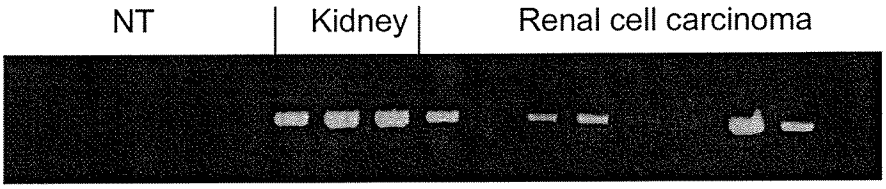
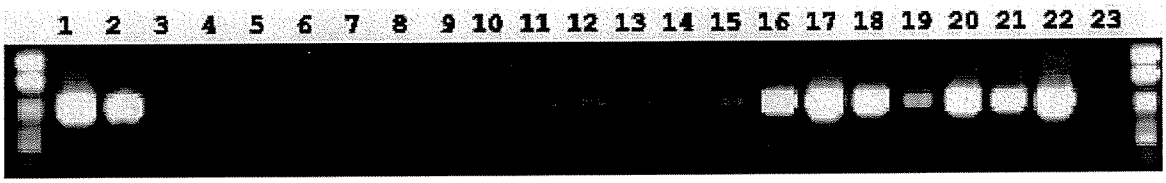


Fig. 16



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Leu Gly Leu Leu Leu Asn Ser Leu Ala Leu Trp Val Phe Cys Cys Arg
35 40 45

Met Gln Gln Trp Thr Glu Thr Arg Ile Tyr Met Thr Asn Leu Ala Val
50 55 60

Ala Asp Leu Cys Leu Leu Cys Thr Leu Pro Phe Val Leu His Ser Leu
65 70 75 80

Arg Asp Thr Ser Asp Thr Pro Leu Cys Gln Leu Ser Gln Gly Ile Tyr
85 90 95

Leu Thr Asn Arg Tyr Met Ser Ile Ser Leu Val Thr Ala Ile Ala Val
100 105 110

Asp Arg Tyr Val Ala Val Arg His Pro Leu Arg Ala Arg Gly Leu Arg

115 120 125

Ser Pro Arg Gln Ala Ala Ala Val Cys Ala Val Leu Trp Val Leu Val
130 135 140

Ile Gly Ser Leu Val Ala Arg Trp Leu Leu Gly Ile Gln Glu Gly Gly
145 150 155 160

Phe Cys Phe Arg Ser Thr Arg His Asn Phe Asn Ser Met Arg Phe Pro
165 170 175

Leu Leu Gly Phe Tyr Leu Pro Leu Ala Val Val Val Phe Cys Ser Leu
180 185 190

Lys Val Val Thr Ala Leu Ala Gln Arg Pro Pro Thr Asp Val Gly Gln
195 200 205

Ala Glu Ala Thr Arg Lys Ala Ala Arg Met Val Trp Ala Asn Leu Leu
210 215 220

Val Phe Val Val Cys Phe Leu Pro Leu His Val Gly Leu Thr Val Arg
225 230 235 240

Leu Ala Val Gly Trp Asn Ala Cys Ala Leu Leu Glu Thr Ile Arg Arg
245 250 255

Ala Leu Tyr Ile Thr Ser Lys Leu Ser Asp Ala Asn Cys Cys Leu Asp
260 265 270

Ala Ile Cys Tyr Tyr Tyr Met Ala Lys Glu Phe Gln Glu Ala Ser Ala
275 280 285

Leu Ala Val Ala Pro Arg Ala Lys Ala His Lys Ser Gln Asp Ser Leu
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Cys Val Thr Leu Ala
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20 25 30

Ala Pro Met Leu Ser Leu Arg Ser Phe Val Phe Val Gly Val Gly Ser
35 40 45

Gly Leu Thr Ser Ser His Ile Pro Ala Gln Arg Trp Ala Glu Trp Gly
50 55 60

Gln Cys Leu Ala Pro Pro Ala Arg Ser Leu Leu Thr Ser Gly Ser Leu
65 70 75 80

Cys Cys Pro Arg Thr Met Asn Gly Thr Tyr Asn Thr Cys Gly Ser Ser
85 90 95

Asp Leu Thr Trp Pro Pro Ala Ile Lys Leu Gly Phe Tyr Ala Tyr Leu
100 105 110

Gly Val Leu Leu Val Leu Gly Leu Leu Leu Asn Ser Leu Ala Leu Trp
115 120 125

Val Phe Cys Cys Arg Met Gln Gln Trp Thr Glu Thr Arg Ile Tyr Met
130 135 140

Thr Asn Leu Ala Val Ala Asp Leu Cys Leu Leu Cys Thr Leu Pro Phe
145 150 155 160

Val Leu His Ser Leu Arg Asp Thr Ser Asp Thr Pro Leu Cys Gln Leu
165 170 175

Ser Gln Gly Ile Tyr Leu Thr Asn Arg Tyr Met Ser Ile Ser Leu Val
180 185 190

Thr Ala Ile Ala Val Asp Arg Tyr Val Ala Val Arg His Pro Leu Arg
195 200 205

Ala Arg Gly Leu Arg Ser Pro Arg Gln Ala Ala Ala Val Cys Ala Val
210 215 220

Leu Trp Val Leu Val Ile Gly Ser Leu Val Ala Arg Trp Leu Leu Gly
225 230 235 240

Ile Gln Glu Gly Gly Phe Cys Phe Arg Ser Thr Arg His Asn Phe Asn
245 250 255

Ser Met Ala Phe Pro Leu Leu Gly Phe Tyr Leu Pro Leu Ala Val Val
260 265 270

Val Phe Cys Ser Leu Lys Val Val Thr Ala Leu Ala Gln Arg Pro Pro
275 280 285

Thr Asp Val Gly Gln Ala Glu Ala Thr Arg Lys Ala Ala Arg Met Val
290 295 300

Trp Ala Asn Leu Leu Val Phe Val Val Cys Phe Leu Pro Leu His Val
305 310 315 320

Gly Leu Thr Val Arg Leu Ala Val Gly Trp Asn Ala Cys Ala Leu Leu
325 330 335

Glu Thr Ile Arg Arg Ala Leu Tyr Ile Thr Ser Lys Leu Ser Asp Ala
340 345 350

Asn Cys Cys Leu Asp Ala Ile Cys Tyr Tyr Tyr Met Ala Lys Glu Phe
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Gly Ser Tyr Glu Ile Ser Val Leu Met Met Gly Asn Ser Ala Phe Ala
35 40 45

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50 55 60

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225 230 235 240

Arg Lys Ser Asn Val Ile Ile Met Cys Gly Gly Pro Glu Phe Leu Tyr
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Val Asp Leu Phe Asn Asp Gln Tyr Leu Glu Asp Asn Val Thr Ala Pro
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Asp Tyr Met Lys Asn Val Leu Val Leu Thr Leu Ser Pro Gly Asn Ser
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Leu Leu Asn Ser Ser Phe Ser Arg Asn Leu Ser Pro Thr Lys Arg Asp
305 310 315 320

Phe Ala Leu Ala Tyr Leu Asn Gly Ile Leu Leu Phe Gly His Met Leu
325 330 335

Lys Ile Phe Leu Glu Asn Gly Glu Asn Ile Thr Thr Pro Lys Phe Ala
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His Ala Phe Arg Asn Leu Thr Phe Glu Gly Tyr Asp Gly Pro Val Thr
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Val Asn Lys Thr Tyr Pro Val Asp Met Ser Pro Thr Phe Thr Trp Lys
405 410 415

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435 440 445

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Gln Lys Lys Trp Ser His Ile Pro Pro Glu Asn Ile Phe Pro Leu Glu
465 470 475 480

Thr Asn Glu Thr Asn His Val Ser Leu Lys Ile Asp Asp Asp Lys Arg
485 490 495

Arg Asp Thr Ile Gln Arg Leu Arg Gln Cys Lys Tyr Asp Lys Lys Arg
500 505 510

Val Ile Leu Lys Asp Leu Lys His Asn Asp Gly Asn Phe Thr Glu Lys
515 520 525

Gln Lys Ile Glu Leu Asn Lys Leu Leu Gln Ile Asp Tyr Tyr Asn Leu
530 535 540

Thr Lys Phe Tyr Gly Thr Val Lys Leu Asp Thr Met Ile Phe Gly Val
545 550 555 560

Ile Glu Tyr Cys Glu Arg Gly Ser Leu Arg Glu Val Leu Asn Asp Thr
565 570 575

Ile Ser Tyr Pro Asp Gly Thr Phe Met Asp Trp Glu Phe Lys Ile Ser
580 585 590

Val Leu Tyr Asp Ile Ala Lys Gly Met Ser Tyr Leu His Ser Ser Lys
595 600 605

Thr Glu Val His Gly Arg Leu Lys Ser Thr Asn Cys Val Val Asp Ser
610 615 620

Arg Met Val Val Lys Ile Thr Asp Phe Gly Cys Asn Ser Ile Leu Pro
625 630 635 640

Pro Lys Lys Asp Leu Trp Thr Ala Pro Glu His Leu Arg Gln Ala Asn
645 650 655

Ile Ser Gln Lys Gly Asp Val Tyr Ser Tyr Gly Ile Ile Ala Gln Glu
660 665 670

Ile Ile Leu Arg Lys Glu Thr Phe Tyr Thr Leu Ser Cys Arg Asp Arg
675 680 685

Asn Glu Lys Ile Phe Arg Val Glu Asn Ser Asn Gly Met Lys Pro Phe
690 695 700

Arg Pro Asp Leu Phe Leu Glu Thr Ala Glu Glu Lys Glu Leu Glu Val
705 710 715 720

Tyr Leu Leu Val Lys Asn Cys Trp Glu Glu Asp Pro Glu Lys Arg Pro
725 730 735

Asp Phe Lys Lys Ile Glu Thr Thr Leu Ala Lys Ile Phe Gly Leu Phe
740 745 750

His Asp Gln Lys Asn Glu Ser Tyr Met Asp Thr Leu Ile Arg Arg Leu
755 760 765

Gln Leu Tyr Ser Arg Asn Leu Glu His Leu Val Glu Glu Arg Thr Gln
770 775 780

Leu Tyr Lys Ala Glu Arg Asp Arg Ala Asp Arg Leu Asn Phe Met Leu
785 790 795 800

Leu Pro Arg Leu Val Val Lys Ser Leu Lys Glu Lys Gly Phe Val Glu
805 810 815

Pro Glu Leu Tyr Glu Glu Val Thr Ile Tyr Phe Ser Asp Ile Val Gly
820 825 830

Phe Thr Thr Ile Cys Lys Tyr Ser Thr Pro Met Glu Val Val Asp Met
835 840 845

Leu Asn Asp Ile Tyr Lys Ser Phe Asp His Ile Val Asp His His Asp

850 855 860

Val Tyr Lys Val Glu Thr Ile Gly Asp Ala Tyr Met Val Ala Ser Gly
865 870 875 880

Leu Pro Lys Arg Asn Gly Asn Arg His Ala Ile Asp Ile Ala Lys Met
885 890 895

Ala Leu Glu Ile Leu Ser Phe Met Gly Thr Phe Glu Leu Glu His Leu
900 905 910

Pro Gly Leu Pro Ile Trp Ile Arg Ile Gly Val His Ser Gly Pro Cys
915 920 925

Ala Ala Gly Val Val Gly Ile Lys Met Pro Arg Tyr Cys Leu Phe Gly
930 935 940

Asp Thr Val Asn Thr Ala Ser Arg Met Glu Ser Thr Gly Leu Pro Leu
945 950 955 960

Arg Ile His Val Ser Gly Ser Thr Ile Ala Ile Leu Lys Arg Thr Glu
965 970 975

Cys Gln Phe Leu Tyr Glu Val Arg Gly Glu Thr Tyr Leu Lys Gly Arg
980 985 990

Gly Asn Glu Thr Thr Tyr Trp Leu Thr Gly Met Lys Asp Gln Lys Phe
995 1000 1005

Asn Leu Pro Thr Pro Pro Thr Val Glu Asn Gln Gln Arg Leu Gln
1010 1015 1020

Ala Glu Phe Ser Asp Met Ile Ala Asn Ser Leu Gln Lys Arg Gln
1025 1030 1035

Ala Ala Gly Ile Arg Ser Gln Lys Pro Arg Arg Val Ala Ser Tyr
1040 1045 1050

Lys Lys Gly Thr Leu Glu Tyr Leu Gln Leu Asn Thr Thr Asp Lys
1055 1060 1065

Glu Ser Thr Tyr Phe
1070

<210> 12
<211> 111
<212> PRT
<213> Homo sapiens

<400> 12

Met Lys Thr Leu Leu Leu Asp Leu Ala Leu Trp Ser Leu Leu Phe Gln
1 5 10 15

Pro Gly Trp Leu Ser Phe Ser Ser Gln Val Ser Gln Asn Cys His Asn
20 25 30

Gly Ser Tyr Glu Ile Ser Val Leu Met Met Gly Asn Ser Ala Phe Ala
35 40 45

Glu Pro Leu Lys Asn Leu Glu Asp Ala Val Asn Glu Gly Leu Glu Ile
50 55 60

Val Arg Gly Arg Leu Gln Asn Ala Gly Leu Asn Val Thr Val Asn Ala
65 70 75 80

Thr Phe Met Tyr Ser Asp Gly Leu Ile His Asn Ser Gly Asp Cys Arg
85 90 95

Ser Ser Thr Cys Glu Gly Leu Asp Leu Leu Arg Lys Ile Ser Pro
100 105 110

<210> 13
<211> 258
<212> PRT
<213> Homo sapiens

<400> 13

Met Lys Thr Leu Leu Leu Asp Leu Ala Leu Trp Ser Leu Leu Phe Gln
1 5 10 15

Pro Gly Trp Leu Ser Phe Ser Ser Gln Val Ser Gln Asn Cys His Asn
20 25 30

Gly Ser Tyr Glu Ile Ser Val Leu Met Met Gly Asn Ser Ala Phe Ala
35 40 45

Glu Pro Leu Lys Asn Leu Glu Asp Ala Val Asn Glu Gly Leu Glu Ile
50 55 60

Val Arg Gly Arg Leu Gln Asn Ala Gly Leu Asn Val Thr Val Asn Ala
65 70 75 80

Thr Phe Met Tyr Ser Asp Gly Leu Ile His Asn Ser Gly Asp Cys Arg
85 90 95

Ser Ser Thr Cys Glu Gly Leu Asp Leu Leu Arg Lys Ile Ser Asn Ala

100 105 110

Gln Arg Met Gly Cys Val Leu Ile Gly Pro Ser Cys Thr Tyr Ser Thr
115 120 125

Phe Gln Met Tyr Leu Asp Thr Glu Leu Ser Tyr Pro Met Ile Ser Ala
130 135 140

Gly Ser Phe Gly Leu Ser Cys Asp Tyr Lys Glu Thr Leu Thr Arg Leu
145 150 155 160

Met Ser Pro Ala Arg Lys Leu Met Tyr Phe Leu Val Asn Phe Trp Lys
165 170 175

Thr Asn Asp Leu Pro Phe Lys Thr Tyr Ser Trp Ser Thr Ser Tyr Val
180 185 190

Tyr Lys Asn Gly Thr Glu Thr Glu Asp Cys Phe Trp Tyr Leu Asn Ala
195 200 205

Leu Glu Ala Ser Val Ser Tyr Phe Ser His Glu Leu Gly Phe Lys Val
210 215 220

Val Leu Arg Gln Asp Lys Glu Phe Gln Asp Ile Leu Met Asp His Asn
225 230 235 240

Arg Lys Ser Asn Val Thr Ser Thr Trp Arg Thr Met Ser Gln Pro Leu
245 250 255

Thr Ile

<210> 14
<211> 1070
<212> PRT
<213> Homo sapiens

<400> 14

Met Lys Thr Leu Leu Leu Asp Leu Ala Leu Trp Ser Leu Leu Phe Gln
1 5 10 15

Pro Gly Trp Leu Ser Phe Ser Ser Gln Val Ser Gln Asn Cys His Asn
20 25 30

Gly Ser Tyr Glu Ile Ser Val Leu Met Met Gly Asn Ser Ala Phe Ala
35 40 45

Glu Pro Leu Lys Asn Leu Glu Asp Ala Val Asn Glu Gly Leu Glu Ile

50 55 60

Val Arg Gly Arg Leu Gln Asn Ala Gly Leu Asn Val Thr Val Asn Ala
65 70 75 80

Thr Phe Met Tyr Ser Asp Gly Leu Ile His Asn Ser Gly Asp Cys Arg
85 90 95

Ser Ser Thr Cys Glu Gly Leu Asp Leu Leu Arg Lys Ile Ser Asn Ala
100 105 110

Gln Arg Met Gly Cys Val Leu Ile Gly Pro Ser Cys Thr Tyr Ser Thr
115 120 125

Phe Gln Met Tyr Leu Asp Thr Glu Leu Ser Tyr Pro Met Ile Ser Ala
130 135 140

Gly Ser Phe Gly Leu Ser Cys Asp Tyr Lys Glu Thr Leu Thr Arg Leu
145 150 155 160

Met Ser Pro Ala Arg Lys Leu Met Tyr Phe Leu Val Asn Phe Trp Lys
165 170 175

Thr Asn Asp Leu Pro Phe Lys Thr Tyr Ser Trp Ser Thr Ser Tyr Val
180 185 190

Tyr Lys Asn Gly Thr Glu Thr Glu Asp Cys Phe Trp Tyr Leu Asn Ala
195 200 205

Leu Glu Ala Ser Val Ser Tyr Phe Ser His Glu Leu Gly Phe Lys Val
210 215 220

Val Leu Arg Gln Asp Lys Glu Phe Gln Asp Ile Leu Met Asp His Asn
225 230 235 240

Arg Lys Ser Asn Val Ile Ile Met Cys Gly Gly Pro Glu Phe Leu Tyr
245 250 255

Lys Leu Lys Gly Asp Arg Ala Val Ala Glu Asp Ile Val Ile Ile Leu
260 265 270

Val Asp Leu Phe Asn Asp Gln Tyr Leu Glu Asp Asn Val Thr Ala Pro
275 280 285

Asp Tyr Met Lys Asn Val Leu Val Leu Thr Leu Ser Pro Gly Asn Ser
290 295 300

Leu Leu Asn Ser Ser Phe Ser Arg Asn Leu Ser Pro Thr Lys Arg Asp
305 310 315 320

Phe Ala Leu Ala Tyr Leu Asn Gly Ile Leu Leu Phe Gly His Met Leu
325 330 335

Lys Ile Phe Leu Glu Asn Gly Glu Asn Ile Thr Thr Pro Lys Phe Ala
340 345 350

His Ala Phe Arg Asn Leu Thr Phe Glu Gly Tyr Asp Gly Pro Val Thr
355 360 365

Leu Asp Asp Trp Gly Asp Val Asp Ser Thr Met Val Leu Leu Tyr Thr
370 375 380

Ser Val Asp Thr Lys Lys Tyr Lys Val Leu Leu Thr Tyr Asp Thr His
385 390 395 400

Val Asn Lys Thr Tyr Pro Val Asp Met Ser Pro Thr Phe Thr Trp Lys
405 410 415

Asn Ser Lys Leu Pro Asn Asp Ile Thr Gly Arg Gly Pro Gln Ile Leu
420 425 430

Met Ile Ala Val Phe Thr Leu Thr Gly Ala Val Val Leu Leu Leu Leu
435 440 445

Val Ala Leu Leu Met Leu Arg Lys Tyr Arg Lys Asp Tyr Glu Leu Arg
450 455 460

Gln Lys Lys Trp Ser His Ile Pro Pro Glu Asn Ile Phe Pro Leu Glu
465 470 475 480

Thr Asn Glu Thr Asn His Val Ser Leu Lys Ile Asp Asp Asp Lys Arg
485 490 495

Arg Asp Thr Ile Gln Arg Leu Arg Gln Cys Lys Tyr Asp Lys Lys Arg
500 505 510

Val Ile Leu Lys Asp Leu Lys His Asn Asp Gly Asn Phe Thr Glu Lys
515 520 525

Gln Lys Ile Glu Leu Asn Lys Ile Asp Tyr Tyr Asn Leu Thr Lys Phe
530 535 540

Tyr Gly Thr Val Lys Leu Asp Thr Met Ile Phe Gly Val Ile Glu Tyr
545 550 555 560

Cys Glu Arg Gly Ser Leu Arg Glu Val Leu Asn Asp Thr Ile Ser Tyr
565 570 575

Pro Asp Gly Thr Phe Met Asp Trp Glu Phe Lys Ile Ser Val Leu Tyr
580 585 590

Asp Ile Ala Lys Gly Met Ser Tyr Leu His Ser Ser Lys Thr Glu Val
595 600 605

His Gly Arg Leu Lys Ser Thr Asn Cys Val Val Asp Ser Arg Met Val
610 615 620

Val Lys Ile Thr Asp Phe Gly Cys Asn Ser Ile Leu Pro Pro Lys Lys
625 630 635 640

Asp Leu Trp Thr Ala Pro Glu His Leu Arg Gln Ala Asn Ile Ser Gln
645 650 655

Lys Gly Asp Val Tyr Ser Tyr Gly Ile Ile Ala Gln Glu Ile Ile Leu
660 665 670

Arg Lys Glu Thr Phe Tyr Thr Leu Ser Cys Arg Asp Arg Asn Glu Lys
675 680 685

Ile Phe Arg Val Glu Asn Ser Asn Gly Met Lys Pro Phe Arg Pro Asp
690 695 700

Leu Phe Leu Glu Thr Ala Glu Glu Lys Glu Leu Glu Val Tyr Leu Leu
705 710 715 720

Val Lys Asn Cys Trp Glu Glu Asp Pro Glu Lys Arg Pro Asp Phe Lys
725 730 735

Lys Ile Glu Thr Thr Leu Ala Lys Ile Phe Gly Leu Phe His Asp Gln
740 745 750

Lys Asn Glu Ser Tyr Met Asp Thr Leu Ile Arg Arg Leu Gln Leu Tyr
755 760 765

Ser Arg Asn Leu Glu His Leu Val Glu Glu Arg Thr Gln Leu Tyr Lys
770 775 780

Ala Glu Arg Asp Arg Ala Asp Arg Leu Asn Phe Met Leu Leu Pro Arg
785 790 795 800

Leu Val Val Lys Ser Leu Lys Glu Lys Gly Phe Val Glu Pro Glu Leu
805 810 815

Tyr Glu Glu Val Thr Ile Tyr Phe Ser Asp Ile Val Gly Phe Thr Thr
820 825 830

Ile Cys Lys Tyr Ser Thr Pro Met Glu Val Val Asp Met Leu Asn Asp
835 840 845

Ile Tyr Lys Ser Phe Asp His Ile Val Asp His His Asp Val Tyr Lys
850 855 860

Val Glu Thr Ile Gly Asp Ala Tyr Met Val Ala Ser Gly Leu Pro Lys
865 870 875 880

Arg Asn Gly Asn Arg His Ala Ile Asp Ile Ala Lys Met Ala Leu Glu
885 890 895

Ile Leu Ser Phe Met Gly Thr Phe Glu Leu Glu His Leu Pro Gly Leu
900 905 910

Pro Ile Trp Ile Arg Ile Gly Val His Ser Gly Pro Cys Ala Ala Gly
915 920 925

Val Val Gly Ile Lys Met Pro Arg Tyr Cys Leu Phe Gly Asp Thr Val
930 935 940

Asn Thr Ala Ser Arg Met Glu Ser Thr Gly Leu Pro Leu Arg Ile His
945 950 955 960

Val Ser Gly Ser Thr Ile Ala Ile Leu Lys Arg Thr Glu Cys Gln Phe
965 970 975

Leu Tyr Glu Val Arg Gly Glu Thr Tyr Leu Lys Gly Arg Gly Asn Glu
980 985 990

Thr Thr Tyr Trp Leu Thr Gly Met Lys Asp Gln Lys Phe Asn Leu Pro
995 1000 1005

Thr Pro Pro Thr Val Glu Asn Gln Gln Arg Leu Gln Ala Glu Phe
1010 1015 1020

Ser Asp Met Ile Ala Asn Ser Leu Gln Lys Arg Gln Ala Ala Gly
1025 1030 1035

Ile Arg Ser Gln Lys Pro Arg Arg Val Ala Ser Tyr Lys Lys Gly
1040 1045 1050

Thr Leu Glu Tyr Leu Gln Leu Asn Thr Thr Asp Lys Glu Ser Thr

1055 1060 1065

Tyr Phe
1070

<210> 15
<211> 93
<212> PRT
<213> Homo sapiens

<400> 15

Met Lys Leu Val Thr Ile Phe Leu Leu Val Thr Ile Ser Leu Cys Ser
1 5 10 15

Tyr Ser Ala Thr Ala Lys Leu Ile Asn Lys Cys Pro Leu Pro Val Asp
20 25 30

Lys Leu Ala Pro Leu Pro Leu Asp Asn Ile Leu Pro Phe Met Asp Pro
35 40 45

Leu Lys Leu Leu Leu Lys Thr Leu Gly Ile Ser Val Glu His Leu Val
50 55 60

Glu Gly Leu Arg Lys Cys Val Asn Glu Leu Gly Pro Glu Ala Ser Glu
65 70 75 80

Ala Val Lys Lys Leu Leu Glu Ala Leu Ser His Leu Val
85 90

<210> 16
<211> 261
<212> PRT
<213> Homo sapiens

<400> 16

Met Ala Val Thr Ala Cys Gln Gly Leu Gly Phe Val Val Ser Leu Ile
1 5 10 15

Gly Ile Ala Gly Ile Ile Ala Ala Thr Cys Met Asp Gln Trp Ser Thr
20 25 30

Gln Asp Leu Tyr Asn Asn Pro Val Thr Ala Val Phe Asn Tyr Gln Gly
35 40 45

Leu Trp Arg Ser Cys Val Arg Glu Ser Ser Gly Phe Thr Glu Cys Arg
50 55 60

Gly Tyr Phe Thr Leu Leu Gly Leu Pro Ala Met Leu Gln Ala Val Arg
65 70 75 80

Ala Leu Met Ile Val Gly Ile Val Leu Gly Ala Ile Gly Leu Leu Val
85 90 95

Ser Ile Phe Ala Leu Lys Cys Ile Arg Ile Gly Ser Met Glu Asp Ser
100 105 110

Ala Lys Ala Asn Met Thr Leu Thr Ser Gly Ile Met Phe Ile Val Ser
115 120 125

Gly Leu Cys Ala Ile Ala Gly Val Ser Val Phe Ala Asn Met Leu Val
130 135 140

Thr Asn Phe Trp Met Ser Thr Ala Asn Met Tyr Thr Gly Met Gly Gly
145 150 155 160

Met Val Gln Thr Val Gln Thr Arg Tyr Thr Phe Gly Ala Ala Leu Phe
165 170 175

Val Gly Trp Val Ala Gly Gly Leu Thr Leu Ile Gly Gly Val Met Met
180 185 190

Cys Ile Ala Cys Arg Gly Leu Ala Pro Glu Glu Thr Asn Tyr Lys Ala
195 200 205

Val Ser Tyr His Ala Ser Gly His Ser Val Ala Tyr Lys Pro Gly Gly
210 215 220

Phe Lys Ala Ser Thr Gly Phe Gly Ser Asn Thr Lys Asn Lys Lys Ile
225 230 235 240

Tyr Asp Gly Gly Ala Arg Thr Glu Asp Glu Val Gln Ser Tyr Pro Ser
245 250 255

Lys His Asp Tyr Val
260

<210> 17
<211> 10
<212> PRT
<213> Homo sapiens

<400> 17

Asp Gln Trp Ser Thr Gln Asp Leu Tyr Asn
1 5 10

<210> 18
<211> 11

<212> PRT
<213> Homo sapiens

<400> 18

Asn Asn Pro Val Thr Ala Val Phe Asn Tyr Gln
1 5 10

<210> 19
<211> 47
<212> PRT
<213> Homo sapiens

<400> 19

Met Ala Val Thr Ala Cys Gln Gly Leu Gly Phe Val Val Ser Leu Ile
1 5 10 15

Gly Ile Ala Gly Ile Ile Ala Ala Thr Cys Met Asp Gln Trp Ser Thr
20 25 30

Gln Asp Leu Tyr Asn Asn Pro Val Thr Ala Val Phe Asn Tyr Gln
35 40 45

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<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 20
aggtacatga gcatcagcct g 21

<210> 21
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 21
gcagcagttg gcatctgaga g 21

<210> 22
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 22
gcaatagaca ttgccaagat g 21

<210> 23
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 23
aacgctgttg attctccaca g 21

<210> 24
<211> 33
<212> DNA
<213> Künstliche Sequenz

<400> 24
ggatcctcct ttagttccca ggtgagtcag aac 33

<210> 25
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 25
tgctctggag gctagcgttt c 21

<210> 26
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 26
accaatcatg ttagcctcaa g 21

<210> 27
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 27
agctatggga tcatcgcaca g 21

<210> 28
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 28
cctttgagct ggagcatctt c 21

<210> 29
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 29
ctttctagct ggagacatca g 21

<210> 30
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 30
caccatggta ctgtcaacat c 21

<210> 31
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<212> DNA
<213> Künstliche Sequenz

<400> 31
atgtcataca agacagagat c 21

<210> 32
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 32
tctgccttgt acagctgtgt c 21

<210> 33
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 33
tctgtggtat tcagctgcaa g 21

<210> 34
<211> 22
<212> DNA
<213> Künstliche Sequenz

<400> 34
tactcaggaa aatttcacct tg 22

<210> 35
<211> 27
<212> DNA
<213> Künstliche Sequenz

<400> 35
gaccacaaca ggaaaagcaa tgtgacc 27

<210> 36
<211> 22
<212> DNA
<213> Künstliche Sequenz

<400> 36
gatagaattg aacaagattg ac 22

<210> 37
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 37
cagcctttgt agttactctg c 21

<210> 38
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 38
tgtcacacca agtgtgatag c 21

<210> 39
<211> 28
<212> DNA
<213> Künstliche Sequenz

<400> 39
ggttcgtggt ttcactgatt gggattgc 28

<210> 40
<211> 27
<212> DNA
<213> Künstliche Sequenz

<400> 40
cggctttgta gttggtttct tctggtg 27

<210> 41
<211> 3814
<212> DNA
<213> Homo sapiens

<400> 41
ctattgaagc cacctgctca ggacaatgaa attcttcagt tacattctgg tttatcgccg 60

atttctcttc gtggttttca ctgtgttggt tttactacct ctgcccatcg tcctccacac 120

caaggaagca gaatgtgcct acacactctt tgtggtcgcc acattttggc tcacagaagc 180

attgcctctg tcggtaacag ctttgctacc tagtttaatg ttacccatgt ttgggatcat 240

gccttctaag aaggtggcat ctgcttattt caaggatttt cacttactgc taattggagt 300

tatctgttta gcaacatcca tagaaaaatg gaatttgcac aagagaattg ctctgaaaat 360

ggtgatgatg gttggtgtaa atcctgcatg gctgacgctg gggttcatga gcagcactgc 420

ctttttgtct atgtggctca gcaacacctc gacggctgcc atggtgatgc ccattgcgga 480

ggctgtagtg cagcagatca tcaatgcaga agcagaggtc gaggccactc agatgactta 540

cttcaacgga tcaaccaacc acggactaga aattgatgaa agtgttaatg gacatgaaat 600

aaatgagagg aaagagaaaa caaaaccagt tccaggatac aataatgata cagggaaaat 660

ttcaagcaag gtggagttgg aaaagaactc aggcatgaga accaaatatc gaacaaagaa 720

gggccacgtg acacgtaaac ttacgtgttt gtgcattgcc tactcttcta ccattggtgg 780

actgacaaca atcactggta cctccaccaa cttgatcttt gcagagtatt tcaatacacg 840

ctatcctgac tgtcgttgcc tcaactttgg atcatggttt acgttttcct tcccagctgc 900

ccttatcatt ctactcttat cctggatctg gcttcagtgg cttttcctag gattcaattt 960

taaggagatg ttcaaatgtg gcaaaaccaa aacagtccaa caaaaagctt gtgctgaggt 1020

gattaagcaa gaataccaaa agcttgggcc aataaggtat caagaaattg tgaccttggt 1080

cctcttcatt ataatggctc tgctatggtt tagtcgagac cccggatttg ttcctggttg 1140

gtctgcactt ttttcagagt accctggttt tgctacagat tcaactgttg ctttacttat 1200

agggctgcta ttctttctta tcccagctaa gacactgact aaaactacac ctacaggaga 1260

aattgttgct tttgattact ctccactgat tacttggaaa gaattccagt cattcatgcc 1320

ctgggatata gccattcttg ttggtggagg gtttgccctg gcagatggtt gtgaggagtc 1380

tggattatct aagtggatag gaaataaatt atctcctctg ggttcattac cagcatggct 1440

aataattctg atatcttctt tgatggtgac atctttaact gaggtagcca gcaatccagc 1500

taccattaca ctctttctcc caatattatc tccattggcc gaagccattc atgtgaaccc 1560

tctttatatt ctgatacctt ctactctgtg tacttcattt gcattcctcc taccagtagc 1620

aaatccaccc aatgctattg tcttttcata tggtcatctg aaagtcattg acatggttaa 1680

agctggactt ggtgtcaaca ttgttggtgt tgctgtggtt atgcttggca tatgtacttg 1740

gattgtaccc atgtttgacc tctacactta cccttcgtgg gctcctgcta tgagtaatga 1800

gaccatgcca taataagcac aaaatttctg actatcttgc ggtaatttct ggaagacatt 1860

aatgattgac tgtaaaatgt ggctctaaat aactaatgac acacatttaa atcagttatg 1920

gtgtagctgc tgcaattccc gtgaataccc gaaacctgct ggtataactc agagtccata 1980

tttgttattg cagtgcaact aaagagcatc tatgtgcctt catcaagaag cccatgtttt 2040

gagattttgc tcatgaacca tctgcaactt gcttcatcat aagaataatt tataacttga 2100

ccttcaaaga gattagagca tttgtttcat cttacagttg gagttcaatg taacatttta 2160

aatgcaattt attatttcag aaatttccca tgaaactaaa aatagaaaat aagatataca 2220

agttaattcg gtacttggat aaatcatttc tgcattgttg ttccagagaa tttgctgaga 2280

aatcaaagcc atggtcatct ggtgatgaag agaaaaggtt aatctaaatg atatgtgcat 2340

ttcctcattt aaaaaatcca attggattat tcttaatata tacatgtaat atgaaaattg 2400

agattgaagc actaattcca aaattatggc tgaatatact aaataacaga aaagttacag 2460

ataagaattt atttctactg aactctatag ttagtgtaat ataattcata tttttatgat 2520

attggcacac tgagaaattc attttgtaga gctatggata aggcttgcta tgatttgcac 2580

tattagtaca gtatagttag aaaggaaagc tgaacactat aaaactatta acatattttc 2640

gtatatgagt aacaactttg cttaagtgtt tatcttagtt cagaaataca taatgtcata 2700

tgttaaaaat aaagagatgt agaaatctaa atgaattatc actgtgtata cagacagaaa 2760

aatcacataa ctctggtgtg ttaacattgc aatgaaaaaa tgaaaaaaag aaggaaaaaa 2820

gaataagaat gaaaactgct gacgtattac aaaacagaaa aataaatgat ttaaaatcaa 2880

atcaaaaaga aaaaaactaa acatttaaac aaaaatggga taagaatagt cttctagaag 2940

tgaggatgcg taaaagaatg agtttccaat taccctgatg tgacaattac acattgtaga 3000

caggtagcaa aatatcacat acacccccaa aatatgtaca aatattatat atcaataaat 3060

aaatttttaa agagtaagtg ctattggcat tccaaaattc agctaaagga aaaatgatca 3120

aaaacaaagt aaggtgcaca gttagcaaaa gatgcagatg ttatatcaca gcaattctca 3180

tgctaaaaat acaacaaaag acaaagcaaa aaataaacct ttgctttttt ttttttttt 3240

ttttttttt gagacggagt ctcgctctgt cgcccaggct ggagtgcagt ggcgggatct 3300

cggctcactg caagctccgc ctcccaggtt cacgccattc tcctgcctca gccaaacctt 3360

tgctattttt aatcttcgtt ggcactttcc agctgttact gaccttgtca ttttttgttc 3420

aaataagatt atttacaaac ttattcttga aactaaatat agtaaagagg gtttttaaaa 3480

taatatttaa catacgaatt attaattggc catgttcatt atttatctat gtttattaat 3540

gggccaatgc aaaaaatcat tttttcaaag aaaaatttgt ccatgtaaag cttaaattat 3600

aatattgctg ctttgtataa ctcttctatg tttattctat tcatttgttc ctttccctac 3660

catattttac acatgtattt ataatctgta gtatttatta catttctgct tttttctagt 3720

cattcaattt atcactgctg aattgcatca gatcatggat gcatttttat tatgaaaaaa 3780

taaaatgact tttcaaatta aaaaaaaaaa aaaa 3814

<210> 42
<211> 734
<212> DNA
<213> Homo sapiens

<400> 42
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aacaaaacca gttccaggat acaataatga tacagggaaa atttcaagca aggtggagtt 660

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<212> DNA
<213> Homo sapiens

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caagatggct ccccatctcc ctctgtccat tctgtatcgc agctagctgc tcaaggaaag 240

gagaaagtgg aaggcatatg tacttagaaa ttattctatt actttcctgg atttaagagt 300

attcagattt tctatttcaa catcaaacaa ttgcattttt aaaaagaaat ttatgtgttc 360

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<211> 556
<212> DNA
<213> Homo sapiens

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tacgttccaa ttagtcctta ttgcatttgt aataaaatcc gcatactttc ggactggcta 540

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<211> 595
<212> PRT
<213> Homo sapiens

<400> 45

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Val Phe Thr Val Leu Val Leu Leu Pro Leu Pro Ile Val Leu His Thr
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Lys Glu Ala Glu Cys Ala Tyr Thr Leu Phe Val Val Ala Thr Phe Trp
35 40 45

Leu Thr Glu Ala Leu Pro Leu Ser Val Thr Ala Leu Leu Pro Ser Leu
50 55 60

Met Leu Pro Met Phe Gly Ile Met Pro Ser Lys Lys Val Ala Ser Ala
65 70 75 80

Tyr Phe Lys Asp Phe His Leu Leu Leu Ile Gly Val Ile Cys Leu Ala
85 90 95

Thr Ser Ile Glu Lys Trp Asn Leu His Lys Arg Ile Ala Leu Lys Met
100 105 110

Val Met Met Val Gly Val Asn Pro Ala Trp Leu Thr Leu Gly Phe Met
115 120 125

Ser Ser Thr Ala Phe Leu Ser Met Trp Leu Ser Asn Thr Ser Thr Ala
130 135 140

Ala Met Val Met Pro Ile Ala Glu Ala Val Val Gln Gln Ile Ile Asn
145 150 155 160

Ala Glu Ala Glu Val Glu Ala Thr Gln Met Thr Tyr Phe Asn Gly Ser
165 170 175

Thr Asn His Gly Leu Glu Ile Asp Glu Ser Val Asn Gly His Glu Ile
180 185 190

Asn Glu Arg Lys Glu Lys Thr Lys Pro Val Pro Gly Tyr Asn Asn Asp
195 200 205

Thr Gly Lys Ile Ser Ser Lys Val Glu Leu Glu Lys Asn Ser Gly Met
210 215 220

Arg Thr Lys Tyr Arg Thr Lys Lys Gly His Val Thr Arg Lys Leu Thr
225 230 235 240

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Cys Leu Cys Ile Ala Tyr Ser Ser Thr Ile Gly Gly Leu Thr Thr Ile
                245                 250                 255

Thr Gly Thr Ser Thr Asn Leu Ile Phe Ala Glu Tyr Phe Asn Thr Arg
            260                 265                 270

Tyr Pro Asp Cys Arg Cys Leu Asn Phe Gly Ser Trp Phe Thr Phe Ser
        275                 280                 285

Phe Pro Ala Ala Leu Ile Ile Leu Leu Leu Ser Trp Ile Trp Leu Gln
    290                 295                 300

Trp Leu Phe Leu Gly Phe Asn Phe Lys Glu Met Phe Lys Cys Gly Lys
305                 310                 315                 320

Thr Lys Thr Val Gln Gln Lys Ala Cys Ala Glu Val Ile Lys Gln Glu
                325                 330                 335

Tyr Gln Lys Leu Gly Pro Ile Arg Tyr Gln Glu Ile Val Thr Leu Val
            340                 345                 350

Leu Phe Ile Ile Met Ala Leu Leu Trp Phe Ser Arg Asp Pro Gly Phe
        355                 360                 365

Val Pro Gly Trp Ser Ala Leu Phe Ser Glu Tyr Pro Gly Phe Ala Thr
    370                 375                 380

Asp Ser Thr Val Ala Leu Leu Ile Gly Leu Leu Phe Phe Leu Ile Pro
385                 390                 395                 400

Ala Lys Thr Leu Thr Lys Thr Thr Pro Thr Gly Glu Ile Val Ala Phe
                405                 410                 415

Asp Tyr Ser Pro Leu Ile Thr Trp Lys Glu Phe Gln Ser Phe Met Pro
            420                 425                 430

Trp Asp Ile Ala Ile Leu Val Gly Gly Gly Phe Ala Leu Ala Asp Gly
        435                 440                 445

Cys Glu Glu Ser Gly Leu Ser Lys Trp Ile Gly Asn Lys Leu Ser Pro
    450                 455                 460

Leu Gly Ser Leu Pro Ala Trp Leu Ile Ile Leu Ile Ser Ser Leu Met
465                 470                 475                 480

Val Thr Ser Leu Thr Glu Val Ala Ser Asn Pro Ala Thr Ile Thr Leu
                485                 490                 495
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Phe Leu Pro Ile Leu Ser Pro Leu Ala Glu Ala Ile His Val Asn Pro
500 505 510

Leu Tyr Ile Leu Ile Pro Ser Thr Leu Cys Thr Ser Phe Ala Phe Leu
515 520 525

Leu Pro Val Ala Asn Pro Pro Asn Ala Ile Val Phe Ser Tyr Gly His
530 535 540

Leu Lys Val Ile Asp Met Val Lys Ala Gly Leu Gly Val Asn Ile Val
545 550 555 560

Gly Val Ala Val Val Met Leu Gly Ile Cys Thr Trp Ile Val Pro Met
565 570 575

Phe Asp Leu Tyr Thr Tyr Pro Ser Trp Ala Pro Ala Met Ser Asn Glu
580 585 590

Thr Met Pro
595

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<211> 224
<212> PRT
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<400> 46

Arg Thr Met Lys Phe Phe Ser Tyr Ile Leu Val Tyr Arg Arg Phe Leu
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Phe Val Val Phe Thr Val Leu Val Leu Leu Pro Leu Pro Ile Val Leu
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His Thr Lys Glu Ala Glu Cys Ala Tyr Thr Leu Phe Val Val Ala Thr
35 40 45

Phe Trp Leu Thr Glu Ala Leu Pro Leu Ser Val Thr Ala Leu Leu Pro
50 55 60

Ser Leu Met Leu Pro Met Phe Gly Ile Met Pro Ser Lys Lys Val Ala
65 70 75 80

Ser Ala Tyr Phe Lys Asp Phe His Leu Leu Leu Ile Gly Val Ile Cys
85 90 95

Leu Ala Thr Ser Ile Glu Lys Trp Asn Leu His Lys Arg Ile Ala Leu
100 105 110

Lys Met Val Met Met Val Gly Val Asn Pro Ala Trp Leu Thr Leu Gly
115 120 125

Phe Met Ser Ser Thr Ala Phe Leu Ser Met Trp Leu Ser Asn Thr Ser
130 135 140

Thr Ala Ala Met Val Met Pro Ile Ala Glu Ala Val Val Gln Gln Ile
145 150 155 160

Ile Asn Ala Glu Ala Glu Val Glu Ala Thr Gln Met Thr Tyr Phe Asn
165 170 175

Gly Ser Thr Asn His Gly Leu Glu Ile Asp Glu Ser Val Asn Gly His
180 185 190

Glu Ile Asn Glu Arg Lys Glu Lys Thr Lys Pro Val Pro Gly Tyr Asn
195 200 205

Asn Asp Thr Gly Lys Ile Ser Ser Lys Val Glu Leu Glu Lys Thr Val
210 215 220

<210> 47
<211> 88
<212> PRT
<213> Homo sapiens

<400> 47

Ala Thr Gln Met Thr Tyr Phe Asn Gly Ser Thr Asn His Gly Leu Glu
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Ile Asp Glu Ser Val Asn Gly His Glu Ile Asn Glu Arg Lys Glu Lys
20 25 30

Thr Lys Pro Val Pro Gly Tyr Asn Asn Asp Thr Gly Lys Ile Ser Ser
35 40 45

Lys Val Glu Leu Glu Lys His Trp Lys Leu Ala Val Gln Asp Gly Ser
50 55 60

Pro Ser Pro Ser Val His Ser Val Ser Gln Leu Ala Ala Gln Gly Lys
65 70 75 80

Glu Lys Val Glu Gly Ile Cys Thr
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<210> 48
<211> 112
<212> PRT

<213> Homo sapiens

<400> 48

His Gly Leu Glu Ile Asp Glu Ser Val Asn Gly His Glu Ile Asn Glu
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Arg Lys Glu Lys Thr Lys Pro Val Pro Gly Tyr Asn Asn Asp Thr Gly
20 25 30

Lys Ile Ser Ser Lys Val Glu Leu Glu Lys Asn Ser Gly Met Arg Thr
35 40 45

Lys Tyr Arg Thr Lys Lys Gly His Val Thr Arg Lys Leu Thr Cys Leu
50 55 60

Cys Ile Ala Tyr Ser Ser Thr Ile Gly Gly Leu Thr Thr Ile Thr Gly
65 70 75 80

Thr Ser Thr Asn Leu Ile Phe Ala Glu Tyr Phe Asn Thr Phe His Pro
85 90 95

His Arg Arg Gly Asp Arg Thr Arg His Val His Gln Glu Ala Glu Ile
100 105 110

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<210> 50
<211> 21
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<400> 50
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<210> 51
<211> 3311
<212> DNA
<213> Homo sapiens

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tatttacaag tacgcaattt gagactaaga tattgttatc attctcctat tgaagacaag 180

agcaatagta aaacacatca ggtcaggggg ttaaagacct gtgataaacc acttccgata 240

agttggaaac gtgtgtctat attttcatat ctgtatatat ataatggtaa agaaagacac 300

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ctcattcagc tgaacaacaa tggctatgaa ggcattgtcg ttgcaatcga ccccaatgtg 480

ccagaagatg aaacactcat tcaacaaata aaggacatgg tgacccaggc atctctgtat 540

ctgtttgaag ctacaggaaa gcgattttat ttcaaaaatg ttgccatttt gattcctgaa 600

acatggaaga caaaggctga ctatgtgaga ccaaaacttg agacctacaa aaatgctgat 660

gttctggttg ctgagtctac tcctccaggt aatgatgaac cctacactga gcagatgggc 720

aactgtggag agaagggtga aaggatccac ctcactcctg atttcattgc aggaaaaaag 780

ttagctgaat atggaccaca aggtaaggca tttgtccatg agtgggctca tctacgatgg 840

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Leu Ile Gln Gln Ile Lys Asp Met Val Thr Gln Ala Ser Leu Tyr Leu
50 55 60

Phe Glu Ala Thr Gly Lys Arg Phe Tyr Phe Lys Asn Val Ala Ile Leu
65 70 75 80

Ile Pro Glu Thr Trp Lys Thr Lys Ala Asp Tyr Val Arg Pro Lys Leu
85 90 95

Glu Thr Tyr Lys Asn Ala Asp Val Leu Val Ala Glu Ser Thr Pro Pro
100 105 110

Gly Asn Asp Glu Pro Tyr Thr Glu Gln Met Gly Asn Cys Gly Glu Lys
115 120 125

Gly Glu Arg Ile His Leu Thr Pro Asp Phe Ile Ala Gly Lys Lys Leu
130 135 140

Ala Glu Tyr Gly Pro Gln Gly Lys Ala Phe Val His Glu Trp Ala His
145 150 155 160

Leu Arg Trp Gly Val Phe Asp Glu Tyr Asn Asn Asp Glu Lys Phe Tyr
165 170 175

```
Leu Ser Asn Gly Arg Ile Gln Ala Val Arg Cys Ser Ala Gly Ile Thr
            180                 185                 190

Gly Thr Asn Val Val Lys Lys Cys Gln Gly Gly Ser Cys Tyr Thr Lys
        195                 200                 205

Arg Cys Thr Phe Asn Lys Val Thr Gly Leu Tyr Glu Lys Gly Cys Glu
    210                 215                 220

Phe Val Leu Gln Ser Arg Gln Thr Glu Lys Ala Ser Ile Met Phe Ala
225                 230                 235                 240

Gln His Val Asp Ser Ile Val Glu Phe Cys Thr Glu Gln Asn His Asn
                245                 250                 255

Lys Glu Ala Pro Asn Lys Gln Asn Gln Lys Cys Asn Leu Arg Ser Thr
            260                 265                 270

Trp Glu Val Ile Arg Asp Ser Glu Asp Phe Lys Lys Thr Thr Pro Met
        275                 280                 285

Thr Thr Gln Pro Pro Asn Pro Thr Phe Ser Leu Leu Gln Ile Gly Gln
    290                 295                 300

Arg Ile Val Cys Leu Val Leu Asp Lys Ser Gly Ser Met Ala Thr Gly
305                 310                 315                 320

Asn Arg Leu Asn Arg Leu Asn Gln Ala Gly Gln Leu Phe Leu Leu Gln
                325                 330                 335

Thr Val Glu Leu Gly Ser Trp Val Gly Met Val Thr Phe Asp Ser Ala
            340                 345                 350

Ala His Val Gln Ser Glu Leu Ile Gln Ile Asn Ser Gly Ser Asp Arg
        355                 360                 365

Asp Thr Leu Ala Lys Arg Leu Pro Ala Ala Ala Ser Gly Gly Thr Ser
    370                 375                 380

Ile Cys Ser Gly Leu Arg Ser Ala Phe Thr Val Ile Arg Lys Lys Tyr
385                 390                 395                 400

Pro Thr Asp Gly Ser Glu Ile Val Leu Leu Thr Asp Gly Glu Asp Asn
                405                 410                 415

Thr Ile Ser Gly Cys Phe Asn Glu Val Lys Gln Ser Gly Ala Ile Ile
```

420 425 430

His Thr Val Ala Leu Gly Pro Ser Ala Ala Gln Glu Leu Glu Glu Leu
435 440 445

Ser Lys Met Thr Gly Gly Leu Gln Thr Tyr Ala Ser Asp Gln Val Gln
450 455 460

Asn Asn Gly Leu Ile Asp Ala Phe Gly Ala Leu Ser Ser Gly Asn Gly
465 470 475 480

Ala Val Ser Gln Arg Ser Ile Gln Leu Glu Ser Lys Gly Leu Thr Leu
485 490 495

Gln Asn Ser Gln Trp Met Asn Gly Thr Val Ile Val Asp Ser Thr Val
500 505 510

Gly Lys Asp Thr Leu Phe Leu Ile Thr Trp Thr Thr Gln Pro Pro Gln
515 520 525

Ile Leu Leu Trp Asp Pro Ser Gly Gln Lys Gln Gly Gly Phe Val Val
530 535 540

Asp Lys Asn Thr Lys Met Ala Tyr Leu Gln Ile Pro Gly Ile Ala Lys
545 550 555 560

Val Gly Thr Trp Lys Tyr Ser Leu Gln Ala Ser Ser Gln Thr Leu Thr
565 570 575

Leu Thr Val Thr Ser Arg Ala Ser Asn Ala Thr Leu Pro Pro Ile Thr
580 585 590

Val Thr Ser Lys Thr Asn Lys Asp Thr Ser Lys Phe Pro Ser Pro Leu
595 600 605

Val Val Tyr Ala Asn Ile Arg Gln Gly Ala Ser Pro Ile Leu Arg Ala
610 615 620

Ser Val Thr Ala Leu Ile Glu Ser Val Asn Gly Lys Thr Val Thr Leu
625 630 635 640

Glu Leu Leu Asp Asn Gly Ala Gly Ala Asp Ala Thr Lys Asp Asp Gly
645 650 655

Val Tyr Ser Arg Tyr Phe Thr Thr Tyr Asp Thr Asn Gly Arg Tyr Ser
660 665 670

Val Lys Val Arg Ala Leu Gly Gly Val Asn Ala Ala Arg Arg Arg Val
675 680 685

Ile Pro Gln Gln Ser Gly Ala Leu Tyr Ile Pro Gly Trp Ile Glu Asn
690 695 700

Asp Glu Ile Gln Trp Asn Pro Pro Arg Pro Glu Ile Asn Lys Asp Asp
705 710 715 720

Val Gln His Lys Gln Val Cys Phe Ser Arg Thr Ser Ser Gly Gly Ser
725 730 735

Phe Val Ala Ser Asp Val Pro Asn Ala Pro Ile Pro Asp Leu Phe Pro
740 745 750

Pro Gly Gln Ile Thr Asp Leu Lys Ala Glu Ile His Gly Gly Ser Leu
755 760 765

Ile Asn Leu Thr Trp Thr Ala Pro Gly Asp Asp Tyr Asp His Gly Thr
770 775 780

Ala His Lys Tyr Ile Ile Arg Ile Ser Thr Ser Ile Leu Asp Leu Arg
785 790 795 800

Asp Lys Phe Asn Glu Ser Leu Gln Val Asn Thr Thr Ala Leu Ile Pro
805 810 815

Lys Glu Ala Asn Ser Glu Glu Val Phe Leu Phe Lys Pro Glu Asn Ile
820 825 830

Thr Phe Glu Asn Gly Thr Asp Leu Phe Ile Ala Ile Gln Ala Val Asp
835 840 845

Lys Val Asp Leu Lys Ser Glu Ile Ser Asn Ile Ala Arg Val Ser Leu
850 855 860

Phe Ile Pro Pro Gln Thr Pro Pro Glu Thr Pro Ser Pro Asp Glu Thr
865 870 875 880

Ser Ala Pro Cys Pro Asn Ile His Ile Asn Ser Thr Ile Pro Gly Ile
885 890 895

His Ile Leu Lys Ile Met Trp Lys Trp Ile Gly Glu Leu Gln Leu Ser
900 905 910

Ile Ala

<210> 61
<211> 501
<212> PRT
<213> Homo sapiens

<400> 61

Met Lys Lys Glu Gly Arg Lys Arg Trp Lys Arg Lys Glu Asp Lys Lys
1 5 10 15

Arg Val Val Val Ser Asn Leu Leu Phe Glu Gly Trp Ser His Lys Glu
20 25 30

Asn Pro Asn Arg His His Arg Gly Asn Gln Ile Lys Thr Ser Lys Tyr
35 40 45

Thr Val Leu Ser Phe Val Pro Lys Asn Ile Phe Glu Gln Leu His Arg
50 55 60

Phe Ala Asn Leu Tyr Phe Val Gly Ile Ala Val Leu Asn Phe Ile Pro
65 70 75 80

Val Val Asn Ala Phe Gln Pro Glu Val Ser Met Ile Pro Ile Cys Val
85 90 95

Ile Leu Ala Val Thr Ala Ile Lys Asp Ala Trp Glu Asp Leu Arg Arg
100 105 110

Tyr Lys Ser Asp Lys Val Ile Asn Asn Arg Glu Cys Leu Ile Tyr Ser
115 120 125

Arg Lys Glu Gln Thr Tyr Val Gln Lys Cys Trp Lys Asp Val Arg Val
130 135 140

Gly Asp Phe Ile Gln Met Lys Cys Asn Glu Ile Val Pro Ala Asp Ile
145 150 155 160

Leu Leu Leu Phe Ser Ser Asp Pro Asn Gly Ile Cys His Leu Glu Thr
165 170 175

Ala Ser Leu Asp Gly Glu Thr Asn Leu Lys Gln Arg Arg Val Val Lys
180 185 190

Gly Phe Ser Gln Gln Glu Val Gln Phe Glu Pro Glu Leu Phe His Asn
195 200 205

Thr Ile Val Cys Glu Lys Pro Asn Asn His Leu Asn Lys Phe Lys Gly
210 215 220

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Tyr Met Glu His Pro Asp Gln Thr Arg Thr Gly Phe Gly Cys Glu Ser
225                 230                 235                 240

Leu Leu Leu Arg Gly Cys Thr Ile Arg Asn Thr Glu Met Ala Val Gly
                245                 250                 255

Ile Val Ile Tyr Ala Gly His Glu Thr Lys Ala Met Leu Asn Asn Ser
            260                 265                 270

Gly Pro Arg Tyr Lys Arg Ser Lys Ile Glu Arg Arg Met Asn Ile Asp
        275                 280                 285

Ile Phe Phe Cys Ile Gly Ile Leu Ile Leu Met Cys Leu Ile Gly Ala
    290                 295                 300

Val Gly His Ser Ile Trp Asn Gly Thr Phe Glu Glu His Pro Pro Phe
305                 310                 315                 320

Asp Val Pro Asp Ala Asn Gly Ser Phe Leu Pro Ser Ala Leu Gly Gly
                325                 330                 335

Phe Tyr Met Phe Leu Thr Met Ile Ile Leu Leu Gln Val Leu Ile Pro
            340                 345                 350

Ile Ser Leu Tyr Val Ser Ile Glu Leu Val Lys Leu Gly Gln Val Phe
        355                 360                 365

Phe Leu Ser Asn Asp Leu Asp Leu Tyr Asp Glu Glu Thr Asp Leu Ser
    370                 375                 380

Ile Gln Cys Arg Ala Leu Asn Ile Ala Glu Asp Leu Gly Gln Ile Gln
385                 390                 395                 400

Tyr Ile Phe Ser Asp Lys Thr Gly Thr Leu Thr Glu Asn Lys Met Val
                405                 410                 415

Phe Arg Arg Cys Thr Ile Met Gly Ser Glu Tyr Ser His Gln Glu Asn
            420                 425                 430

Gly Ile Glu Ala Pro Lys Gly Ser Ile Pro Leu Ser Lys Arg Lys Tyr
        435                 440                 445

Pro Ala Leu Leu Arg Asn Glu Glu Ile Lys Asp Ile Leu Leu Ala Leu
    450                 455                 460

Leu Glu Ala Val Trp His Phe His Lys Leu Leu Pro Val Ser Leu Trp
465                 470                 475                 480
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Ser Ser Leu Ser Gln Ile Arg Ala Val Pro Ile Thr Cys Lys Leu Ser
485 490 495

Phe Val Tyr Lys Gly
500

<210> 62
<211> 154
<212> PRT
<213> Homo sapiens

<400> 62

Met Gly Arg Arg Ser Pro Phe Lys Pro Arg Asn Lys Val Phe Gly Phe
1 5 10 15

Ser Tyr Pro Trp Cys Arg Ser Tyr Gln Pro Phe Pro Arg Lys Arg Ala
20 25 30

Trp Pro Pro Ser Arg Val Trp Leu Gly Ala Cys Cys Ala Ser Leu Ala
35 40 45

Ser Pro Pro Lys Gly Thr Ile Pro Ser Gly Glu Tyr Tyr Arg Pro Ala
50 55 60

Pro Ser Ser Ser Gly Asp Ser Leu Arg Arg Glu Ser Gly Ala Leu Leu
65 70 75 80

Gln Tyr Leu Pro Ser Leu Ala Ser Pro Cys Ala Asn His Ala Thr Arg
85 90 95

Cys Ser Leu Leu Phe Pro Ile Tyr Lys Ile Lys Met Thr Leu Leu Tyr
100 105 110

Leu Thr Gly Leu Ala Arg Thr His Cys Cys Cys Leu Ala Asp Arg Cys
115 120 125

Ala Glu Ala Val Glu Ser Ala Phe Tyr Leu Val Gly Ser Leu Cys Ile
130 135 140

Asn Ala Arg Gly Ala Ala His Leu Thr Asp
145 150

<210> 63
<211> 484
<212> PRT
<213> Homo sapiens

<400> 63

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Met Ala Gly Pro Trp Thr Phe Thr Leu Leu Cys Gly Leu Leu Ala Ala
1               5                  10                  15

Thr Leu Ile Gln Ala Thr Leu Ser Pro Thr Ala Val Leu Ile Leu Gly
            20                  25                  30

Pro Lys Val Ile Lys Glu Lys Leu Thr Gln Glu Leu Lys Asp His Asn
        35                  40                  45

Ala Thr Ser Ile Leu Gln Gln Leu Pro Leu Leu Ser Ala Met Arg Glu
    50                  55                  60

Lys Pro Ala Gly Gly Ile Pro Val Leu Gly Ser Leu Val Asn Thr Val
65                  70                  75                  80

Leu Lys His Ile Ile Trp Leu Lys Val Ile Thr Ala Asn Ile Leu Gln
                85                  90                  95

Leu Gln Val Lys Pro Ser Ala Asn Asp Gln Glu Leu Leu Val Lys Ile
            100                 105                 110

Pro Leu Asp Met Val Ala Gly Phe Asn Thr Pro Leu Val Lys Thr Ile
        115                 120                 125

Val Glu Phe His Met Thr Thr Glu Ala Gln Ala Thr Ile Arg Met Asp
    130                 135                 140

Thr Ser Ala Ser Gly Pro Thr Arg Leu Val Leu Ser Asp Cys Ala Thr
145                 150                 155                 160

Ser His Gly Ser Leu Arg Ile Gln Leu Leu His Lys Leu Ser Phe Leu
                165                 170                 175

Val Asn Ala Leu Ala Lys Gln Val Met Asn Leu Leu Val Pro Ser Leu
            180                 185                 190

Pro Asn Leu Val Lys Asn Gln Leu Cys Pro Val Ile Glu Ala Ser Phe
        195                 200                 205

Asn Gly Met Tyr Ala Asp Leu Leu Gln Leu Val Lys Val Pro Ile Ser
    210                 215                 220

Leu Ser Ile Asp Arg Leu Glu Phe Asp Leu Leu Tyr Pro Ala Ile Lys
225                 230                 235                 240

Gly Asp Thr Ile Gln Leu Tyr Leu Gly Ala Lys Leu Leu Asp Ser Gln
                245                 250                 255
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Gly Lys Val Thr Lys Trp Phe Asn Asn Ser Ala Ala Ser Leu Thr Met
260 265 270

Pro Thr Leu Asp Asn Ile Pro Phe Ser Leu Ile Val Ser Gln Asp Val
275 280 285

Val Lys Ala Ala Val Ala Ala Val Leu Ser Pro Glu Glu Phe Met Val
290 295 300

Leu Leu Asp Ser Val Leu Pro Glu Ser Ala His Arg Leu Lys Ser Ser
305 310 315 320

Ile Gly Leu Ile Asn Glu Lys Ala Ala Asp Lys Leu Gly Ser Thr Gln
325 330 335

Ile Val Lys Ile Leu Thr Gln Asp Thr Pro Glu Phe Phe Ile Asp Gln
340 345 350

Gly His Ala Lys Val Ala Gln Leu Ile Val Leu Glu Val Phe Pro Ser
355 360 365

Ser Glu Ala Leu Arg Pro Leu Phe Thr Leu Gly Ile Glu Ala Ser Ser
370 375 380

Glu Ala Gln Phe Tyr Thr Lys Gly Asp Gln Leu Ile Leu Asn Leu Asn
385 390 395 400

Asn Ile Ser Ser Asp Arg Ile Gln Leu Met Asn Ser Gly Ile Gly Trp
405 410 415

Phe Gln Pro Asp Val Leu Lys Asn Ile Ile Thr Glu Ile Ile His Ser
420 425 430

Ile Leu Leu Pro Asn Gln Asn Gly Lys Leu Arg Ser Gly Val Pro Val
435 440 445

Ser Leu Val Lys Ala Leu Gly Phe Glu Ala Ala Glu Ser Ser Leu Thr
450 455 460

Lys Asp Ala Leu Val Leu Thr Pro Ala Ser Leu Trp Lys Pro Ser Ser
465 470 475 480

Pro Val Ser Gln

<210> 64

<211> 256
<212> PRT
<213> Homo sapiens

<400> 64

Met Phe Gln Thr Gly Gly Leu Ile Val Phe Tyr Gly Leu Leu Ala Gln
1 5 10 15

Thr Met Ala Gln Phe Gly Gly Leu Pro Val Pro Leu Asp Gln Thr Leu
20 25 30

Pro Leu Asn Val Asn Pro Ala Leu Pro Leu Ser Pro Thr Gly Leu Ala
35 40 45

Gly Ser Leu Thr Asn Ala Leu Ser Asn Gly Leu Leu Ser Gly Gly Leu
50 55 60

Leu Gly Ile Leu Glu Asn Leu Pro Leu Leu Asp Ile Leu Lys Pro Gly
65 70 75 80

Gly Gly Thr Ser Gly Gly Leu Leu Gly Gly Leu Leu Gly Lys Val Thr
85 90 95

Ser Val Ile Pro Gly Leu Asn Asn Ile Ile Asp Ile Lys Val Thr Asp
100 105 110

Pro Gln Leu Leu Glu Leu Gly Leu Val Gln Ser Pro Asp Gly His Arg
115 120 125

Leu Tyr Val Thr Ile Pro Leu Gly Ile Lys Leu Gln Val Asn Thr Pro
130 135 140

Leu Val Gly Ala Ser Leu Leu Arg Leu Ala Val Lys Leu Asp Ile Thr
145 150 155 160

Ala Glu Ile Leu Ala Val Arg Asp Lys Gln Glu Arg Ile His Leu Val
165 170 175

Leu Gly Asp Cys Thr His Ser Pro Gly Ser Leu Gln Ile Ser Leu Leu
180 185 190

Asp Gly Leu Gly Pro Leu Pro Ile Gln Gly Leu Leu Asp Ser Leu Thr
195 200 205

Gly Ile Leu Asn Lys Val Leu Pro Glu Leu Val Gln Gly Asn Val Cys
210 215 220

Pro Leu Val Asn Glu Val Leu Arg Gly Leu Asp Ile Thr Leu Val His

225 230 235 240

Asp Ile Val Asn Met Leu Ile His Gly Leu Gln Phe Val Ile Lys Val
245 250 255

<210> 65
<211> 791
<212> PRT
<213> Homo sapiens

<400> 65

Met Ser Gln Pro Arg Pro Arg Tyr Val Val Asp Arg Ala Ala Tyr Ser
1 5 10 15

Leu Thr Leu Phe Asp Asp Glu Phe Glu Lys Lys Asp Arg Thr Tyr Pro
20 25 30

Val Gly Glu Lys Leu Arg Asn Ala Phe Arg Cys Ser Ser Ala Lys Ile
35 40 45

Lys Ala Val Val Phe Gly Leu Leu Pro Val Leu Ser Trp Leu Pro Lys
50 55 60

Tyr Lys Ile Lys Asp Tyr Ile Ile Pro Asp Leu Leu Gly Gly Leu Ser
65 70 75 80

Gly Gly Ser Ile Gln Val Pro Gln Gly Met Ala Phe Ala Leu Leu Ala
85 90 95

Asn Leu Pro Ala Val Asn Gly Leu Tyr Ser Ser Phe Phe Pro Leu Leu
100 105 110

Thr Tyr Phe Phe Leu Gly Gly Val His Gln Met Val Pro Gly Thr Phe
115 120 125

Ala Val Ile Ser Ile Leu Val Gly Asn Ile Cys Leu Gln Leu Ala Pro
130 135 140

Glu Ser Lys Phe Gln Val Phe Asn Asn Ala Thr Asn Glu Ser Tyr Val
145 150 155 160

Asp Thr Ala Ala Met Glu Ala Glu Arg Leu His Val Ser Ala Thr Leu
165 170 175

Ala Cys Leu Thr Ala Ile Ile Gln Met Gly Leu Gly Phe Met Gln Phe
180 185 190

Gly Phe Val Ala Ile Tyr Leu Ser Glu Ser Phe Ile Arg Gly Phe Met

195 200 205

Thr Ala Ala Gly Leu Gln Ile Leu Ile Ser Val Leu Lys Tyr Ile Phe
210 215 220

Gly Leu Thr Ile Pro Ser Tyr Thr Gly Pro Gly Ser Ile Val Phe Thr
225 230 235 240

Phe Ile Asp Ile Cys Lys Asn Leu Pro His Thr Asn Ile Ala Ser Leu
245 250 255

Ile Phe Ala Leu Ile Ser Gly Ala Phe Leu Val Leu Val Lys Glu Leu
260 265 270

Asn Ala Arg Tyr Met His Lys Ile Arg Phe Pro Ile Pro Thr Glu Met
275 280 285

Ile Val Val Val Val Ala Thr Ala Ile Ser Gly Gly Cys Lys Met Pro
290 295 300

Lys Lys Tyr His Met Gln Ile Val Gly Glu Ile Gln Arg Gly Phe Pro
305 310 315 320

Thr Pro Val Ser Pro Val Val Ser Gln Trp Lys Asp Met Ile Gly Thr
325 330 335

Ala Phe Ser Leu Ala Ile Val Ser Tyr Val Ile Asn Leu Ala Met Gly
340 345 350

Arg Thr Leu Ala Asn Lys His Gly Tyr Asp Val Asp Ser Asn Gln Glu
355 360 365

Met Ile Ala Leu Gly Cys Ser Asn Phe Phe Gly Ser Phe Phe Lys Ile
370 375 380

His Val Ile Cys Cys Ala Leu Ser Val Thr Leu Ala Val Asp Gly Ala
385 390 395 400

Gly Gly Lys Ser Gln Val Ala Ser Leu Cys Val Ser Leu Val Val Met
405 410 415

Ile Thr Met Leu Val Leu Gly Ile Tyr Leu Tyr Pro Leu Pro Lys Ser
420 425 430

Val Leu Gly Ala Leu Ile Ala Val Asn Leu Lys Asn Ser Leu Lys Gln
435 440 445

Leu Thr Asp Pro Tyr Tyr Leu Trp Arg Lys Ser Lys Leu Asp Cys Cys
450 455 460

Ile Trp Val Val Ser Phe Leu Ser Ser Phe Phe Leu Ser Leu Pro Tyr
465 470 475 480

Gly Val Ala Val Gly Val Ala Phe Ser Val Leu Val Val Val Phe Gln
485 490 495

Thr Gln Phe Arg Asn Gly Tyr Ala Leu Ala Gln Val Met Asp Thr Asp
500 505 510

Ile Tyr Val Asn Pro Lys Thr Tyr Asn Arg Ala Gln Asp Ile Gln Gly
515 520 525

Ile Lys Ile Ile Thr Tyr Cys Ser Pro Leu Tyr Phe Ala Asn Ser Glu
530 535 540

Ile Phe Arg Gln Lys Val Ile Ala Lys Thr Gly Met Asp Pro Gln Lys
545 550 555 560

Val Leu Leu Ala Lys Gln Lys Tyr Leu Lys Lys Gln Glu Lys Arg Arg
565 570 575

Met Arg Pro Thr Gln Gln Arg Arg Ser Leu Phe Met Lys Thr Lys Thr
580 585 590

Val Ser Leu Gln Glu Leu Gln Gln Asp Phe Glu Asn Ala Pro Pro Thr
595 600 605

Asp Pro Asn Asn Asn Gln Thr Pro Ala Asn Gly Thr Ser Val Ser Tyr
610 615 620

Ile Thr Phe Ser Pro Asp Ser Ser Ser Pro Ala Gln Ser Glu Pro Pro
625 630 635 640

Ala Ser Ala Glu Ala Pro Gly Glu Pro Ser Asp Met Leu Ala Ser Val
645 650 655

Pro Pro Phe Val Thr Phe His Thr Leu Ile Leu Asp Met Ser Gly Val
660 665 670

Ser Phe Val Asp Leu Met Gly Ile Lys Ala Leu Ala Lys Leu Ser Ser
675 680 685

Thr Tyr Gly Lys Ile Gly Val Lys Val Phe Leu Val Asn Ile His Ala
690 695 700

Gln Val Tyr Asn Asp Ile Ser His Gly Gly Val Phe Glu Asp Gly Ser
705 710 715 720

Leu Glu Cys Lys His Val Phe Pro Ser Ile His Asp Ala Val Leu Phe
725 730 735

Ala Gln Ala Asn Ala Arg Asp Val Thr Pro Gly His Asn Phe Gln Gly
740 745 750

Ala Pro Gly Asp Ala Glu Leu Ser Leu Tyr Asp Ser Glu Glu Asp Ile
755 760 765

Arg Ser Tyr Trp Asp Leu Glu Gln Glu Met Phe Gly Ser Met Phe His
770 775 780

Ala Glu Thr Leu Thr Ala Leu
785 790

<210> 66
<211> 243
<212> PRT
<213> Homo sapiens

<400> 66

Met Glu Gln Gly Ser Gly Arg Leu Glu Asp Phe Pro Val Asn Val Phe
1 5 10 15

Ser Val Thr Pro Tyr Thr Pro Ser Thr Ala Asp Ile Gln Val Ser Asp
20 25 30

Asp Asp Lys Ala Gly Ala Thr Leu Leu Phe Ser Gly Ile Phe Leu Gly
35 40 45

Leu Val Gly Ile Thr Phe Thr Val Met Gly Trp Ile Lys Tyr Gln Gly
50 55 60

Val Ser His Phe Glu Trp Thr Gln Leu Leu Gly Pro Val Leu Leu Ser
65 70 75 80

Val Gly Val Thr Phe Ile Leu Ile Ala Val Cys Lys Phe Lys Met Leu
85 90 95

Ser Cys Gln Leu Cys Lys Glu Ser Glu Glu Arg Val Pro Asp Ser Glu
100 105 110

Gln Thr Pro Gly Gly Pro Ser Phe Val Phe Thr Gly Ile Asn Gln Pro
115 120 125

Ile Thr Phe His Gly Ala Thr Val Val Gln Tyr Ile Pro Pro Pro Tyr
130 135 140

Gly Ser Pro Glu Pro Met Gly Ile Asn Thr Ser Tyr Leu Gln Ser Val
145 150 155 160

Val Ser Pro Cys Gly Leu Ile Thr Ser Gly Gly Ala Ala Ala Ala Met
165 170 175

Ser Ser Pro Pro Gln Tyr Tyr Thr Ile Tyr Pro Gln Asp Asn Ser Ala
180 185 190

Phe Val Val Asp Glu Gly Cys Leu Ser Phe Thr Asp Gly Gly Asn His
195 200 205

Arg Pro Asn Pro Asp Val Asp Gln Leu Glu Glu Thr Gln Leu Glu Glu
210 215 220

Glu Ala Cys Ala Cys Phe Ser Pro Pro Pro Tyr Glu Glu Ile Tyr Ser
225 230 235 240

Leu Pro Arg

<210> 67
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 67
acacgaatgg tagatacagt g 21

<210> 68
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 68
atacttgtga gctgttccat g 21

<210> 69
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 69
actgttacct tgcatggact g 21

<210> 70
<211> 21
<212> DNA

<213> Künstliche Sequenz

<400> 70
caatgagaac acatggacat g 21

<210> 71
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 71
ccatgaaagc tccatgtcta c 21

<210> 72
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 72
agagatggca catattctgt c 21

<210> 73
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 73
atcggctgaa gtcaagcatc g 21

<210> 74
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 74
tggtcagtga ggactcagct g 21

<210> 75
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 75
tttctctgct tgatgcactt g 21

<210> 76
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 76
gtgagcactg ggaagcagct c 21

<210> 77
<211> 21
<212> DNA

<213> Künstliche Sequenz

<400> 77
ggcaaatgct agagacgtga c 21

<210> 78
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 78
aggtgtcctt cagctgccaa g 21

<210> 79
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 79
gttaagtgct ctctggactt g 21

<210> 80
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 80
atcctgattg ctgtgtgcaa g 21

<210> 81
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 81
ctcttctagc tggtcaacat c 21

<210> 82
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 82
ccagcaacaa cttacgtggt c 21

<210> 83
<211> 21
<212> DNA
<213> Künstliche Sequenz

<400> 83
cctttattca cccaatcact c 21

<210> 84
<211> 2165
<212> DNA

<213> Homo sapiens

<400> 84

agaacagcgc agtttgccct ccgctcacgc agagcctctc cgtggcctcc gcaccttgag 60

cattaggcca gttctcctct tctctctaat ccatccgtca cctctcctgt catccgtttc 120

catgccgtga ggtccattca cagaacacat ccatggctct catgctcagt ttggttctga 180

gtctcctcaa gctgggatca gggcagtggc aggtgtttgg gccagacaag cctgtccagg 240

ccttggtggg ggaggacgca gcattctcct gtttcctgtc tcctaagacc aatgcagagg 300

ccatggaagt gcggttcttc aggggccagt tctctagcgt ggtccacctc tacagggacg 360

ggaaggacca gccatttatg cagatgccac agtatcaagg caggacaaaa ctggtgaagg 420

attctattgc ggaggggcgc atctctctga ggctggaaaa cattactgtg ttggatgctg 480

gcctctatgg gtgcaggatt agttcccagt cttactacca gaaggccatc tgggagctac 540

aggtgtcagc actgggctca gttcctctca tttccatcac gggatatgtt gatagagaca 600

tccagctact ctgtcagtcc tcgggctggt tcccccggcc cacagcgaag tggaaaggtc 660

cacaaggaca ggatttgtcc acagactcca ggacaaacag agacatgcat ggcctgtttg 720

atgtggagat ctctctgacc gtccaagaga acgccgggag catatcctgt tccatgcggc 780

atgctcatct gagccgagag gtggaatcca gggtacagat aggagatacc tttttcgagc 840

ctatatcgtg gcacctggct accaaagtac tgggaatact ctgctgtggc ctatttttg 900

gcattgttgg actgaagatt ttcttctcca aattccagtg taagcgagag agagaagcat 960

gggccggtgc cttattcatg gttccagcag ggacaggatc agagatgctc ccacatccag 1020

ctgcttctct tcttctagtc ctagcctcca ggggcccagg cccaaaaaag gaaaatccag 1080

gcggaactgg actggagaag aaagcacgga caggcagaat tgagagacgc ccggaaacac 1140

gcagtggagg tgactctgga tccagagacg gctcacccga agctctgcgt ttctgatctg 1200

aaaactgtaa cccatagaaa agctccccag gaggtgcctc actctgagaa gagatttaca 1260

aggaagagtg tggtggcttc tcagagtttc caagcaggga aacattactg ggaggtggac 1320

ggaggacaca ataaaaggtg gcgcgtggga gtgtgccggg atgatgtgga caggaggaag 1380

gagtacgtga ctttgtctcc cgatcatggg tactgggtcc tcagactgaa tggagaacat 1440

ttgtatttca cattaaatcc ccgttttatc agcgtcttcc ccaggacccc acctacaaaa 1500

ataggggtct tcctggacta tgagtgtggg accatctcct tcttcaacat aaatgaccag 1560

tcccttattt ataccctgac atgtcggttt gaaggcttat tgaggcccta cattgagtat 1620

ccgtcctata atgagcaaaa tggaactccc atagtcatct gcccagtcac ccaggaatca 1680

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Gly Glu Asp Ala Ala Phe Ser Cys Phe Leu Ser Pro Lys Thr Asn Ala
35 40 45

Glu Ala Met Glu Val Arg Phe Phe Arg Gly Gln Phe Ser Ser Val Val
50 55 60

His Leu Tyr Arg Asp Gly Lys Asp Gln Pro Phe Met Gln Met Pro Gln
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Tyr Gln Gly Arg Thr Lys Leu Val Lys Asp Ser Ile Ala Glu Gly Arg
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Ile Ser Leu Arg Leu Glu Asn Ile Thr Val Leu Asp Ala Gly Leu Tyr
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Gly Cys Arg Ile Ser Ser Gln Ser Tyr Tyr Gln Lys Ala Ile Trp Glu
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Leu Gln Val Ser Ala Leu Gly Ser Val Pro Leu Ile Ser Ile Thr Gly
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Tyr Val Asp Arg Asp Ile Gln Leu Leu Cys Gln Ser Ser Gly Trp Phe
145 150 155 160

Pro Arg Pro Thr Ala Lys Trp Lys Gly Pro Gln Gly Gln Asp Leu Ser

165 170 175

Thr Asp Ser Arg Thr Asn Arg Asp Met His Gly Leu Phe Asp Val Glu
180 185 190

Ile Ser Leu Thr Val Gln Glu Asn Ala Gly Ser Ile Ser Cys Ser Met
195 200 205

Arg His Ala His Leu Ser Arg Glu Val Glu Ser Arg Val Gln Ile Gly
210 215 220

Asp Thr Phe Phe Glu Pro Ile Ser Trp His Leu Ala Thr Lys Val Leu
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Gly Ile Leu Cys Cys Gly Leu Phe Phe Gly Ile Val Gly Leu Lys Ile
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Phe Phe Ser Lys Phe Gln Cys Lys Arg Glu Arg Glu Ala Trp Ala Gly
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Ala Leu Phe Met Val Pro Ala Gly Thr Gly Ser Glu Met Leu Pro His
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Pro Ala Ala Ser Leu Leu Leu Val Leu Ala Ser Arg Gly Pro Gly Pro
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Lys Lys Glu Asn Pro Gly Gly Thr Gly Leu Glu Lys Lys Ala Arg Thr
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